Synthesis of Indole-4-carboxaldehydes and 4-Acetylindole from *N*-Alkyl-5-aminoisoquinolinium Salts

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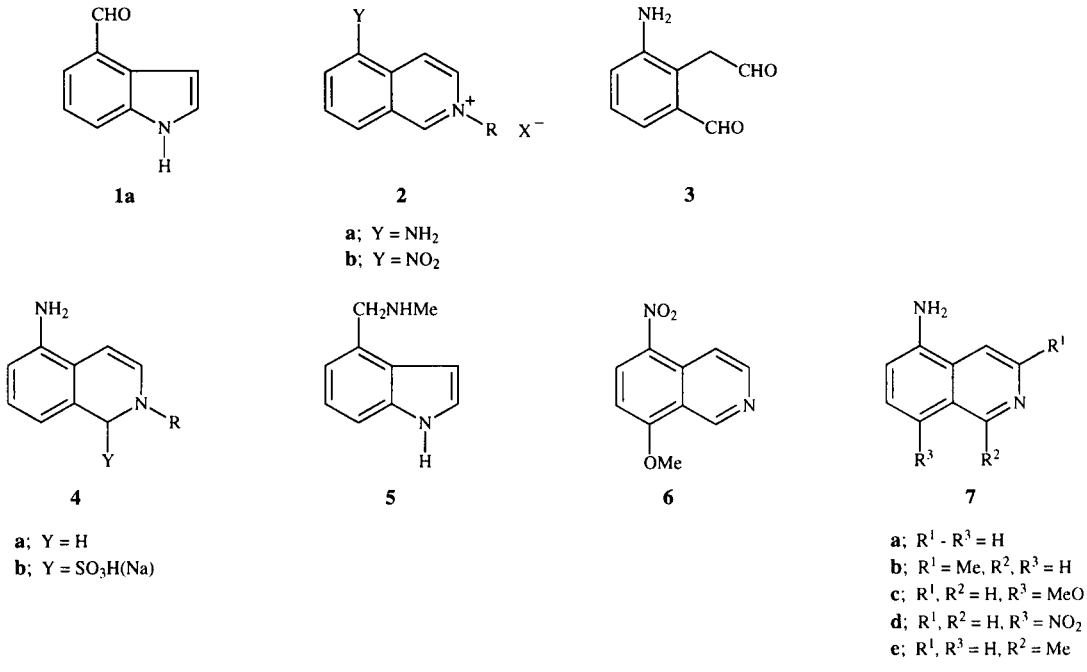
Received December 10, 1999

N-Alkyl-5-aminoisoquinolinium salts (**8a-d**) are converted into indole-4-carboxaldehydes (**1a-c**) on heating in a two phase alkyl acetate-water system containing an excess of a 2:1 sodium bisulfite-sodium sulfite mixture. 4-Acetylindole **1e** is prepared in the same way from 1-methyl-2-cyanomethylisoquinolinium bromide **8f**.

J. Heterocyclic Chem., **37**, 1293 (2000).

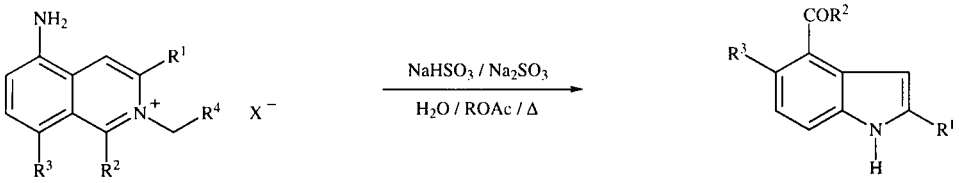
Indole-4-carboxaldehyde (**1a**, Scheme 1) is frequently used as a starting material for the synthesis of various ergot alkaloids [1-9] and compounds of potential medicinal interest [10,11]. It was first prepared in 1955 by Hardegger and Corrodi [12] from 4-alkoxycarbonylindole, and since that time, no less than six distinctly different syntheses of this compound have been devised [11,12-18]. The considerable effort devoted to the generation of this relatively simple compound is an impressive demonstration of its importance as a synthetic intermediate.

Scheme 1



We were intrigued by the possibility that 5-aminoisoquinolinium salts **2a** might serve as a source of indole-4-carboxaldehyde if hydrolytic cleavage of the heterocyclic ring to the homophthaldehyde derivative **3**, or a formal equivalent thereof, could be accomplished. Indeed, such intermediates have often been proposed in many ring cleavage-recyclization reactions of *N*-substituted isoquinolinium salts initiated by nucleophilic reagents such as hydroxide ion, hydroxylamine, hydrazines, *etc.* [19]. In fact, with hydroxide ion as the nucleophilic reagent, mono-protected forms of homophthalaldehyde have on occasion even been isolated [20]. Furthermore, in a process obviously related to the proposed conversion of **2a** to **1a**, Somei, *et al.*, [14] have reported that 4-methylaminomethylindole **5** is obtained in a *ca.* 25% yield by the reduction of 5-nitroisoquinolinium salts **2b** with aqueous titanium trichloride. This transformation presumably proceeds *via* an intermediate 1,2-dihydro-5-aminoisoquinoline **4a**. In this article an efficient, direct transformation of *N*-substituted-5-aminoisoquinolinium salts **8a,b** to indole-4-carboxaldehyde **1a** is described, and the process is extended to the generation of several congeners of **1a**.

Scheme 2



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a; R^1 - R^4 = H, X = I
b; R^1- R^3 = H, R^4 = CN, X = Br
c; R^1 = Me, R^2, R^3 = H, R^4 = CN, X = Br
d; R^1, R^2 = H, R^3 = MeO, R^4 = CN, X = Br
e; R^1, R^2 = H, R^3 = NO_2, R^4 = CN, X = Br
f; R^1, R^3 = H, R^2 = Me, R^4 = CN, X = Br

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a; R^1 - R^3 = H
b; R^1 = Me, R^2, R^3 = H
c; R^1, R^2 = H, R^3 = MeO
d; R^1, R^2 = H, R^3 = NO_2
e; R^1, R^3 = H, R^2 = Me

The 2-alkyl-5-aminoisoquinolinium salts **8** (Scheme 2) used in this study were prepared in good yield from the amines **7** and the appropriate alkyl halide. All the amines except 5-amino-8-methoxyisoquinoline **7c** are known. This very oxidation sensitive substance was obtained by the hydrazine hydrate – Raney nickel reduction [21] of the corresponding nitro compound **6** (see Experimental).

After many futile attempts to convert *N*-methyl-5-aminoisoquinolinium iodide **8a** into indole 4-carboxaldehyde **1a**, or the corresponding oxime, with aqueous hydroxide or hydroxylamine solutions, it was decided that transformations of this type might be more likely to occur if a nucleophilic species could be added to C-1 of **8a** under acidic conditions. Sodium bisulfite was selected as the nucleophilic reagent because of the facile and reversible adduct formation with aldehydes, ketones, and derivatives thereof, and because of the known cleavage reactions of *N*-alkylpyridinium salts mediated by alkylammonium sulfites [22]. The 1,2-dihydroisoquinoline intermediate **4b**, if formed, would be expected to undergo hydrolytic cleavage and cyclization to a 4-substituted indole, as shown by Somei, *et al.* [14]. Heating an aqueous solution of **8a** and sodium bisulfite (3 equivalents) at reflux temperature for 24 hours did produce **1a** in *ca.* 3% yield. The yield of **1a** was doubled if sodium sulfite [23] was also present, and an organic solvent was added to the reaction mixture to remove the aldehyde as it was formed. With isopropyl acetate as the organic phase (reaction temperature 80 °C), the optimum bisulfite:sulfite:**8a** ratio was found to be 20:10:1 and under those conditions **8a** was slowly but cleanly converted into **1a** (73-79%, Table 1) after 192 hours [24,25]. When *n*-butyl acetate was used as the organic phase (reaction temperature 96-98 °C), **1a** was obtained in 82% yield after 96 hours (entry **4**, reaction essentially complete after 72 hours; see Experimental). Furthermore, using *n*-butyl acetate and the isoquinolinium salt **8b**, in which the nuclear *N*-atom bears the electron attracting cyanomethyl moiety, the conversion to **1a** was effectively complete in 48 hours (see Experimental).

Table 1

Conversion of 1-Alkyl-5-aminoisoquinolinium Salts into 4-Acylindoles

Entry	Starting Material	Product	Organic Solvent	Reaction Time, Hours	Yield [a]
1	**8a**	**1a**	*i*-PrOAc	192	73-79
2	**8a**	**1a**	*n*-BuOAc	96	82
3	**8b**	**1a**	*i*-PrOAc	96	73
4	**8b**	**1a**	*n*-BuOAc	72	82
5	**8c**	**1b**	*i*-PrOAc	48	52
6	**8d**	**1c**	*n*-BuOAc	113	42
7	**8e**	**1d**	*n*-BuOAc	72	0
8	**8f**	**1e**	*n*-BuOAc	136	71

[a] Recrystallized yield after indicated time.

The above process is also applicable to the synthesis of congeners of **1a**. Thus, the isoquinolinium salts **8c** and **8d** were converted into 2-methyl- and 5-methoxyindole-4-carboxaldehydes **1b**, and **1c**, respectively (Table 1, entries 5 and 6). In addition, 4-acetylindole **1e** could be obtained in this way from the 1-methylisoquinolinium salt **8f** (Table 1, entry 8). In contrast, although nucleophilic addition to C-1 should be electronically favored for the 8-nitroisoquinolinium salt **8e**, it is inert to conversion into **1d** (Table 1, entry 7). This may be a steric phenomenon, although the isoquinolinium salts **8d**, and **8f**, in which nucleophilic addition to C-1 should be disfavored for both steric and electronic reasons, nevertheless both undergo the expected ring fragmentation-recyclization process.

The two most cost effective and efficient syntheses of **1a** reported to date [5a,b;15f] are of the Leimgruber-Batcho type [26]. Both utilize inexpensive 2-methyl-3-nitrobenzoic acid as the starting material and proceed in 51-53% [15a,b; five steps] and 71% [15f; seven steps] overall yields. The synthesis described herein produces **1a** in 73% yield from commercially available, but expensive, 5-aminoisoquinoline (**7a**). The cost of **7a** surely must be a reflection of demand for this substance since it is easily prepared in two steps (*ca.* 72%) from very inexpensive isoquinoline [27,28]. Thus, the synthesis of **1a** from isoquinoline (~53% overall) could well compare favorably with the Leimgruber-Batcho processes in the future.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were measured as dispersions in KBr on a Nicolet 5PC FT-IR spectrophotometer. The nmr spectra were recorded with a Bruker AMX 300 instrument. 5-Aminoisoquinoline **7a** was obtained from commercial sources. 3-Methyl-5-aminoisoquinoline **7b** [29], 1-methyl-5-aminoisoquinoline **7e** [30], 5-amino-8-nitroisoquinoline **7d** [31], and 2-methyl-5-aminoisoquinolinium iodide **8a** [32] were prepared as described in the references cited.

8-Methoxy-5-nitroisoquinoline (**6**).

8-Methoxyisoquinoline [33] (2.63 g, 16.5 mmoles) was added with stirring to concentrated sulfuric acid (13 mL) at -5 to 0 °C and then a solution of potassium nitrate (1.835 g, 18.15 mmoles) in concentrated sulfuric acid (10 mL) was added thereto at the same temperature (*ca.* 25 minutes). The solution was stirred at -5 to 0 °C for 1 hour, and then the reaction temperature was allowed to reach room temperature over a 1 hour period. The solution was poured onto ice and concentrated ammonium hydroxide was added to the stirred solution, maintaining the temperature below 15 °C, until the *p*H of the mixture reached *ca.* 9. The yellow solid was collected by filtration, washed with cold water, and dried *in vacuo*. This solid was slurried with dichloromethane, the insoluble material was removed by filtration, neutral alumina (Act I, 30 g) was added to the filtrate and the mixture was evaporated to dryness *in vacuo*. This mixture was placed on top of a dry packed column of Act II neutral alumina (370 g, 14 x 6 cm), covered with a small amount of sand, and the column was eluted with 1,2-dichloroethane-ethanol (99:1; 100 mL fractions). Fractions 11-17 contained the product (1.07 g) which was taken up in hot toluene and diluted with an equal volume of hexane. A yellow solid (0.850 g, 25.2% yield) with mp 150-151 °C was obtained. Recrystallization of a portion of this substance from 1:2 toluene-hexane gave material with mp 151-153 °C (lit [34] 154-155 °C) after drying *in vacuo* at 50 °C. ^{1}H nmr ($CDCl_3$) δ 4.19 (s, 3H, OMe), 6.96 (d, 1H, H-7, J = 8.9 Hz), 8.68 (dd, 1H, H-3 or H-4, J = 0.9, 6.3 Hz), 8.77 (bd, 1H, H-4 or H-3, J = 6.3 Hz), 9.74 (d, 1H, H-1, J = 0.9 Hz). This spectrum is similar to, but not identical with that reported [34]. ^{13}C nmr ($CDCl_3$) δ 57.2 (q), 104.3 (d), 116.6 (d), 120.5 (s), 130.8 (s), 132.5 (d), 137.5 (s), 147.0 (d), 148.2 (d), 162.6 (s).

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.76; H, 3.90; N, 13.74.

5-Amino-2-cyanomethylisoquinolinium Bromide (**8b**).

Bromoacetonitrile (2.40 g, 1.4 mL, 20 mmoles) and 5-aminoisoquinoline (2.88 g, 10 mmoles) were dissolved in acetonitrile (95 mL). After filtration to remove a small amount of insoluble material, the solution was left at room temperature for 30 hours during which time much of the product crystallized. The mixture was stirred at reflux temperature for 0.5 hour, and after cooling to room temperature the product was collected by filtration, washed with a little acetonitrile and dried *in vacuo*. This material (4.00 g) had mp 212.5-214.5 °C dec. The mother liquors were evaporated *in vacuo*, the residue was slurried with acetonitrile, and after collection by filtration, *etc.* as above, gave additional product [0.69 g, total yield 4.69 g (89%)] mp 211-213 °C. Both crops of product were sufficiently pure for use in the next step. For analysis the salt was twice crystallized from 90% ethanol to give a brilliant red solid, mp 218-220 °C dec; ir: ν NH_2 3444, 3328 (sh), 3316, 3196, ν CN 2239 (w), ν NO_2 1593, 1576 cm^{-1}; ^{1}H nmr (D_2O): δ 5.77 (m, 0.2H, NCH_2, largely exchanged but intensity augmented on addition of H_2O), 7.21 (dd, 1H, H-6, J = 1.4, 7.4 Hz), 7.50 (bdd, 1H, H-8, J = <1, 1.4, 7.8 Hz), 7.56 (t, 1H, H-7), 8.17 (bd, 1H, H-4, J = <1, 7.1 Hz), 8.28 (dd, 1H, H-3, J = 1.7, 7.1 Hz), 9.50 (d, 1H, H-1, J = 1.7 Hz; ^{13}C nmr (D_2O) δ 116.0 (s), 122.9 (d), 123.5 (d), 124.5 (d), 129.4 (s), 130.9 (s), 134.2 (d), 135.6 (d), 146.1 (s), 153.0 (d).

Anal. Calcd. for $C_{11}H_{10}BrN_3$: C, 50.02; H, 3.82; N, 15.91. Found: C, 50.15; H, 3.73; N, 15.79.

5-Amino-2-cyanomethyl-3-methylisoquinolinium Bromide (**8c**).

A solution of bromoacetonitrile (1.205 g, 0.7 mL, 10.05 mmoles) and 3-methyl-5-aminoisoquinoline [(25), 1.532 g, 10 mmoles)] in acetonitrile (175 mL) was stirred at reflux temperature for 18 hours (product separated from solution after 1 hour). The product was collected by filtration and after drying *in vacuo*, the solid (1.70 g) had mp 243-244.5 °C dec. The mother liquor still contained **7b**, therefore, additional bromoacetonitrile (0.35 mL, 5.025 mmoles) was added and stirring at reflux temperature was maintained for 23 hours. Additional product (0.515 g) was thus obtained [total, 2.215 g (80% yeild)] which had mp 242.5-243.5 °C dec. Both crops of product were sufficiently pure for the next reaction. For analysis, the salt was crystallized from 35% ethanol to give a bright orange solid, mp 244-245 °C dec; ^{1}H nmr (D_2O) δ 3.01 (s, 3H, Me), 5.98 (bm, very weak, exchanged by D_2O, CH_2, appears at δ 6.16 in DMSO-d_6) 7.40 (dd, 1H, H-6, J = 1.6, 7.1 Hz), 7.66 (bdd, 1H, H-8, J = 1.6, 8.3 Hz), 7.73 (t, 1H, H-7), 8.23 (bs, 1H, H-4), 9.65 (s, 1H, H-1); ^{13}C nmr δ 20.6 (q), 114.7 (s), 121.5 (d), 121.9 (d), 123.6 (d), 128.9 (s), 130.1 (s), 133.7 (d), 143.6 (s), 144.2 (s), 152.8 (d). The methylene group was not visible, but appeared at δ 44.8 in DMSO-d_6).

Anal. Calcd. for $C_{12}H_{12}BrN_3$: C, 51.81; H, 4.35; N, 15.11. Found: C, 51.85; H, 4.27; N, 15.12.

5-Amino-2-cyanomethyl-8-methoxyisoquinolinium Bromide (**8d**).

A suspension of activated Raney Nickel in ethanol (*ca.* 0.45 g, which had been washed free of water with ethanol) was added to a solution of 5-nitro-8-methoxyisoquinoline (0.928 g, 4.54 mmoles) in ethanol (75 mL) containing water (0.5 mL, 27.8 mmoles) and maintained under an argon atmosphere. A solution of hydrazine (0.86 mL, 0.878 g, 27.4 mmoles) in ethanol (25 mL) was added over a 10 minute period to the vigorously stirred mixture containing the Raney Nickel catalyst. This mixture was heated slowly to relfux temperature where it was maintained for 2 hours. The mixture was cooled to room temperature, filtered through Celite with minimal exposure to air, and the filtrate was evaporated to dryness *in vacuo*. 5-Amino-8-methoxyisoquinoline **7c** was obtained as an olive green solid which was homogeneous by tlc (alumina, CH_2Cl_2). This material rapidly was converted into an insoluble black solid on exposure to air. Therefore, it was immediately dissolved in acetonitrile (100 mL, argon atmosphere), bromoacetonitrile was added (0.4 mL, 0.681 g, 5.74 mmoles) and the solution was stirred at reflux temperature for 5 hours, after which time further bromoacetonitrile (0.08 mL, 0.138 g, 1.15 mmoles) was added. The mixture was stirred at reflux temperature for 16.5 hours and after cooling to room temperature, the maroon colored solid was collected by filtration, washed with acetonitrile and dried *in vacuo*. This material (0.955 g,

71.5% yield) had mp 217-220 °C dec and was sufficiently pure for the next reaction. For analysis, a sample was twice crystallized from ethanol to give a maroon colored solid mp 218-220 °C dec; ir ν 3421 (NH_2), 1590, 1512 (NO_2) cm^{-1}; ^1H nmr (D_2O) δ 4.08 (s, 3H, OMe), 5.99 (m, partially exchanged, CH_2), 7.25 (d, 1H, H-6 or H-7, J = 8.6 Hz), 7.52 (d, 1H, H-7 or H-6, J = 8.6 Hz), 8.33 (d, 1H, H-4, J = 7.1 Hz), 8.54 (dd, 1H, H-3, J = 1.8, 7.1 Hz), 9.85 (d, 1H, H-1, J = 1.8 Hz); ^{13}C nmr (D_2O) δ 47.5, 57.0 (q), 112.0 (d), 113.9 (s), 119.9 (s), 121.7 (d), 125.2 (d), 127.4 (s), 132.6 (d), 135.7 (s), 146.5 (d), 151.9 (s).

Anal. Calcd. for $C_{12}H_{12}BrN_3O$: C, 48.99; H, 4.11; N, 14.29. Found: C, 48.72; H, 4.17; N, 14.36.

5-Amino-2-cyanomethyl-8-nitroisoquinolinium Bromide (**8e**).

A solution of 5-amino-8-nitroisoquinoline (0.946 g, 5.0 mmoles) and bromoacetonitrile (0.38 mL, 0.654 g, 5.0 mmoles) in acetonitrile (120 mL) was stirred at reflux temperature; a red solid began to separate from solution within 1 hour. After 5 hours, additional bromoacetonitrile (0.19 mL, 0.327 g, 2.73 mmoles) was added and heating at reflux temperature was continued for a total of 22 hours. After cooling to room temperature, the solid was collected by filtration, and dried *in vacuo*. This material (1.184 g, 76.6%) had mp 235-240 °C dec. On crystallization from 80% ethanol, a brilliant deep red crystalline solid, mp 239-241 °C dec was obtained, but further crystallization gave a different allotrope, mp 227-228 °C dec. The ^1H nmr (D_2O) spectra of both allotropes were identical; δ 6.13 (m, largely exchanged, CH_2), 7.21 (d, 1H, H-6, J = 9.1 Hz), 8.75 (d, 1H, H-4, J = 7.0 Hz), 8.81 (d, 1H, H-7, J = 9.2 Hz), 8.82 (dd, 1H, H-3, J = 1.6, 7.0 Hz), 10.77 (d, 1H, H-1, J = 1.6 Hz); ^{13}C nmr (D_2O) δ 51.4, 115.8 (s), 116.7 (d), 125.8 (d), 126.1 (s), 129.2 (s), 134.6 (s), 136.6 (d), 137.7 (d), 150.3 (d), 154.8 (s).

Anal. Calcd. for $C_{11}H_9BrN_4O_2$: C, 42.74; H, 2.93; N, 18.13. Found: C, 42.80; H, 2.94; N, 17.94.

5-Amino-2-cyanomethyl-1-methylisoquinolinium Bromide (**8f**).

A solution of 1-methyl-5-aminoisoquinoline (0.791 g, 5.0 mmoles) in acetonitrile (100 mL) containing bromoacetonitrile (0.35 mL, 0.603 g, 5.03 mmoles) was stirred at reflux temperature. Additional quantities of bromoacetonitrile were added after 3 hours (0.18 mL, 0.310 g, 2.58 mmoles), and 23 hours. After 29 hours, the mixture was cooled to room temperature, the product was collected by filtration, and dried *in vacuo*. The solid (0.910 g, 65.4%) had mp 237.5-238.5 °C dec. This material was sufficiently pure for use in the next reaction. For analysis, a small sample was twice crystallized from 80% ethanol to give a solid which after drying *in vacuo* at 50 °C had mp 240-242 °C dec; ^1H nmr (D_2O) δ 3.32 (s, 3H, Me), 5.97 (s, partially exchanged, CH_2), 7.48 (d, 1H, H-6, J = 7.8 Hz), 7.81 (t, 1H, H-7), 7.98 (d, 1H, H-8, J = 8.5 Hz), 8.29 (d, 1H, H-3 or H-4, J = 7.2 Hz), 8.43 (d, 1H, H-4 or H-3, J = 7.2 Hz); ^{13}C nmr (D_2O) δ 17.7 (q), 57.1 (t), 115.7 (s), 120.9 (d), 122.2 (d), 123.1 (d), 129.4 (s), 131.3 (s), 135.3 (d), 135.7 (d), 146.5 (s), 163.9 (s).

Anal. Calcd. for $C_{12}H_{12}BrN_3$: C, 51.81; H, 4.35; N, 15.11. Found: C, 51.73; H, 4.31, N, 15.00.

Indole-4-carboxaldehyde (**1a**).

A. From 5-Amino-2-methylisoquinolinium Iodide (**8a**).

A solution of **8a** (0.858 g, 3.0 mmoles) in water (60 mL) containing sodium hydrogen sulfite (6.24 g, 60 mmoles) and sodium sulfite (3.78 g, 30 mmoles) was layered with isopropyl acetate (200 mL) and the mixture was stirred at reflux temperature for 96 hours. The organic phase was separated, washed sequentially with 10% HCl solution (to remove traces of **5a**), 10% Na_2CO_3 solution, water, and saturated NaCl solution. After drying (Na_2SO_4) the solvent was removed *in vacuo* leaving 0.272 g of crude **1a**. The aqueous phase from above was layered with isopropyl acetate (200 mL) and the mixture was stirred at reflux temperature for a further 96 hours. The usual workup gave an additional 0.100 g of the product (combined crude yield 85.5%). Crystallization of this material from toluene gave a cream colored solid mp 140-142.5 °C (lit [13] mp 142-144 °C). A mixed mp with authentic material was not depressed. See Table 1 for recrystallized yields.

With *n*-butyl acetate as the organic solvent the reaction times and crude yields were: 47 hours (74%), 72 hours (83%), 96 hours (86%).

B. From 5-Amino-2-cyanomethylisoquinolinium Bromide (**8b**).

The organic solvent, reaction periods and crude yields are given. Isopropyl acetate; 48 hours (64%), 93 hours (82%), *n*-butyl acetate; 48 hours (83%), 72 hours (88%).

2-Methylindole-4-carboxyaldehyde (**1b**).

This compound was prepared in the usual manner from the isoquinolinium salt **8c** using isopropyl acetate as the organic phase and a reaction period of 48 hours. The crude product (63% yield) was twice crystallized from toluene to give a white solid mp 117.5-118.5 °C; ^1H nmr ($CDCl_3$) δ 2.49 (d, 3H, Me J = 0.9 Hz), 7.04 (m, 1H, H-3, J = 0.9, 0.9 Hz), 7.23 (t, 1H, H-6), 7.54 (ddd, 1H, H-7, J = 0.9, 1.0, 8.0 Hz), 7.58 (dd, 1H, H-5, J = 1.0, 7.4 Hz), 8.50 (bs, 1H, exchanged with D_2O, NH), 10.22 (s, 1H, CHO); ^{13}C nmr ($CDCl_3$) δ 14.3 (q), 101.5 (d), 117.0 (d), 120.6 (d), 127.6 (d), 127.7 (s), 137.3 (s), 140.0 (s), 193.8 (d).

Anal. Calcd. for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.77; H, 5.68; N, 8.90.

5-Methoxyindole-4-carboxaldehyde (**1c**).

Prepared in the usual way from **8d** using *n*-butyl acetate as the organic phase. The reaction periods and crude yields were 65 hours (41%), 113 hours (48%). The crude product after two crystallizations from toluene and drying *in vacuo* at 45 °C had mp 146-148 °C (phase change at 136-140 °C). On solidification and remelting the compound melted at 146-148 °C (no phase change); ^1H nmr ($CDCl_3$) δ 3.94 (s, 3H, OMe), 6.86 (d, 1H, H-6, J = 8.9 Hz), 7.36 (q, 2H, H-2, 3, J = 3.3 Hz), 7.59 (d, 1H, H-7, J = 8.9 Hz), 8.74 (bs, 1H, exchanged with D_2O, NH), 10.75 (s, 1H, CHO); ^{13}C nmr ($CDCl_3$) δ 57.3 (q), 104.0 (d), 107.4 (d), 116.2 (s), 119.5 (d), 126.9 (s), 131.9 (d), 143.2 (s), 159.9 (s), 191.6 (d).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.63; H, 5.13; N, 8.08.

4-Acetylindole (**1e**).

Prepared in the usual way from the isoquinolinium salt **8f** using *n*-butyl acetate as the organic phase. The reaction periods and crude yields were 41 hours (48%), 89 hours (70%), 136 hours (78%). Crystallization of the crude product from toluene gave a cream colored solid mp 160-161 °C (lit [35] mp 159-160 °C) mp 160-161 °C with an authentic specimen; ^1H nmr ($CDCl_3$) δ 2.69 (s, 3H, Me), 7.29 (t, 1H, H-6), 7.31 (dd 1H, H-3, J = 0.8, 3.2 Hz), 7.34 (d, 1H, H-2, J = 3.2 Hz), 7.59 (dt, 1H, H-7, J = 0.8, 0.8, 8.1 Hz), 7.73 (dd, 1H, H-5, J = 0.8, 7.5 Hz), 9.60 (bs, 1H, exchanged with D_2O, NH).

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[25] Isoquinolinium salt **7a** was also converted into **1a** by excess methylammonium sulfide [22], but the transformation was even slower (66% crude yield after 192 hous) and the purity of **1a** was inferior (50% yield after crystallization).

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