A New Synthesis of 1-Alkyl-3-aminoindoles

Maria Luisa SACCARELLO, Riccardo STRADI*

Istituto di Chimica Organica della Facoltà di Farmacia, Università di Milano, Viale Abruzzi 42, I-20131 Milano, Italy

The diimmonium dibromides **1**, which are easy to prepare from 1,2-diaminoethenes **2** by addition of bromine[1] or, more practically, by reaction of 1,1,2,2-tetraaminoethanes **3** with acetyl bromide[2], have attracted some attention in recent years.

Although their behaviour towards nucleophiles has been extensively studied[3], the approach to their utilization in the synthesis of nitrogen-containing five-membered ring het-

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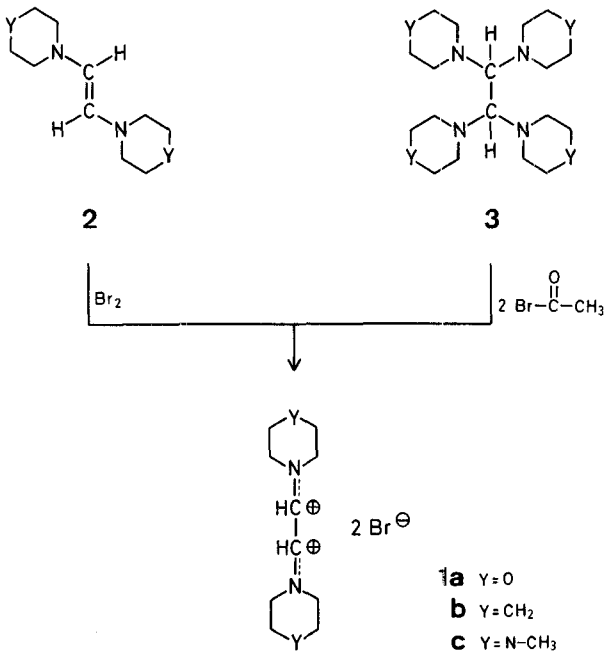
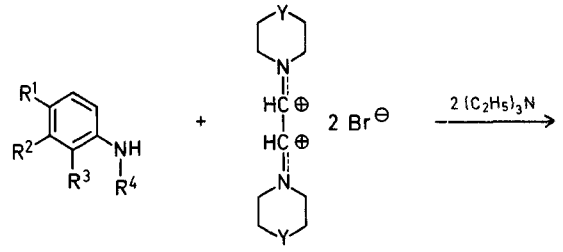
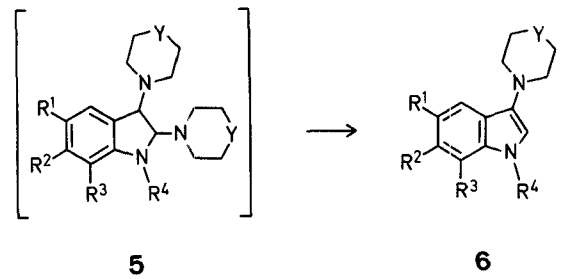
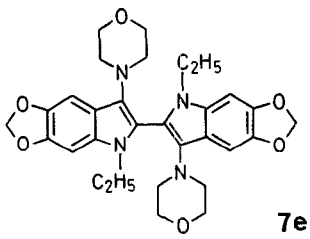


erocycles has just begun and, as far as we are aware, only the preparation of some 2-imidazoline derivatives has been described[4].

We now wish to report a new entry to 1-alkyl-3-aminoindoles **6** directly from *N*-alkylanilines **4** and the diimmonium salt **1**. The reaction probably proceeds via an unstable 2,3-diamino intermediate **5** which easily undergoes aromatization through elimination of an amino group.



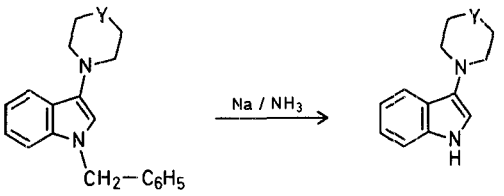




In addition to 3-morpholino-5,6-methylenedioxyindole (**6e**), the coupled oxidation product **7e** was isolated in a small amount.

Our attempts to obtain 3-aminoindoles unsubstituted at nitrogen starting from primary anilines have not been successful; only complex reaction mixtures were obtained in this case.

However, we have found that 1-benzyl-3-morpholino-indole (**6d**) undergoes debenzylation on treatment with sodium in liquid ammonia to afford 3-morpholinoindole (**8**) in almost quantitative yield.



Diimmonium Dibromides 1a–c:
These compounds are prepared by the reaction of the corresponding 1,1,2,2-tetraaminoethanes **3** with acetyl bromide according to Ref. [2].

***N*-Alkylanilines 4; General Procedure:**
To a stirred solution of the aniline (0.06 mol) in ethanol (200 ml), Raney Nickel (~20 g) is added. The reaction mixture is stirred under reflux until a G.L.C. (column SE 30 10%, T. column 150°, T. ev. 300°; carrier N_2; flow rate 30 ml/min) control shows the disappearance of the aniline. Raney Nickel is then filtered on kieselgur and the filtrate is freed from ethanol under vacuo. The crude oily residue is distilled under reduced pressure.

N-Ethyl-3,4-methylenedioxyaniline; yield: 9.4 g (95%); b.p. 104°/2 torr (Lit. [5] 101–103°/ torr).

N-Ethyl-4-fluoroaniline; yield: 8.1 g (97%); b.p. 96°/25 torr (Lit. [6] 92°/14 torr).

N-Ethyl-3-(trifluoromethyl)-aniline; yield: 9.9 g (87%); b.p. 98°/25 torr (Lit. [5] 53–54°/5 torr).

N-Ethyl-2,4-difluoroaniline; yield: 8.7 g (93%); b.p. 76–78°/25 torr.

1-Alkyl-3-aminoindoles 6; General Procedure:
To a suspension of freshly prepared diimmonium dibromide **1** (0.01 mol) in dry dichloromethane (80 ml), a solution of freshly distilled *N*-alkylaniline **4** (0.01 mol) and triethylamine (2.02 g, 0.02 mol) dissolved in dry dichloromethane (40 ml) is added. The mixture is stirred at room temperature for 3 h, washed twice with water, the organic layer is dried with anhydrous sodium sulphate, and the solvent removed under reduced pressure to give the crude aminoindole **6**. The product is purified by column chromatography on silica gel (ratio silica gel/crude product 40:1) using the eluents shown in the Table.

2,2'-Bi-(1-ethyl-5,6-methylenedioxy-3-morpholino)-indolyl (7e):
The crude indole **6e** (2.0 g) is column chromatographed on silica gel (ratio silica gel/crude product 80:1). Elution with diethyl ether affords, before the main product **6e**, a white crystalline powder; yield: 249 mg (7%); m.p. 199° (from diisopropyl ether).

$C_{30}H_{34}N_4O_6$	calc.	C 65.92	H 6.27	N 10.25
(546.6)	found	65.7	6.3	10.1

M.S.: *m/e* (relative intensity) = 546 (M^+, 100%).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.2 (t, 6H, CH_3); 2.93–3.23 (m, 8H, CH_2—N—CH_2); 3.4–4.07 (m, 12H, CH_2—O—CH_2, CH_2—CH_3); 5.97 (s, 4H, O—CH_2—O); 6.85, 7.17 ppm (2s, $4H_{arom.}$).

able. 1-Alkyl-3-aminoindoles **6**

roduct lo.	R^1	R^2	R^3	R^4	Y	Eluent for chromatography	Yield[a] [%]	m.p.[b] (solvent)	Molecular formula[c] or Lit. m.p.	^{1}H-N.M.R. ($CDCl_3$/TMS)[d] δ [ppm]
a	H	H	H	CH_3	CH_2	C_6H_6/C_2H_5OAc, 90:10	68	76–77° (PE)	75–76°[7]	1.33–2.05 [m, 6H, $-(CH_2)_3-$]; 2.73–3.23 (m, 4H, CH_2-N-CH_2); 3.56 (s, 3H, CH_3); 6.5 (s, 1H, H-2); 6.83–7.35 (m, 3H, H-5, H-6, H-7); 7.5–7.83 (m, 1H, H-4)
b	H	H	H	CH_3	O	C_6H_6/C_2H_5OAc, 80:20	75	82° [$(i\text{-}C_3H_7)_2O$]	$C_{13}H_{16}N_2O$ (216.3)	3.0 (t, 4H, $-CH_2-N-CH_2-$); 3.6 (s, 3H, CH_3); 3.9 (t, 4H, $-CH_2-O-CH_2-$); 6.5 (s, 1H, H-2); 6.9–7.36 (m, 3H, H-5, H-6, H-7); 7.43–7.8 (m, 1H, H-4)
c	H	H	H	C_2H_5	O	C_6H_6/C_2H_5OAc, 80:20	82	46–47° ($n\text{-}C_5H_{12}$)	$C_{14}H_{18}N_2O$ (230.3)	1.4 (t, 3H, CH_3); 2.83–3.3 (m, 4H, $-CH_2-N-CH_2-$); 3.6–4.3 (m, 6H, $-CH_2-O-CH_2-$, CH_2CH_3); 6.63 (s, 1H, H-2); 6.9–7.43 (m, 3H, H-5, H-6, H-7); 7.45–7.8 (m, 1H, H-4)
d	H	H	H	$C_6H_5CH_2$	O	C_6H_6/C_2H_5OAc, 80:20	56	b.p. 200–202°/ 0.2 torr	$C_{19}H_{20}N_2O$ (292.4)	2.9–3.23 (m, 4H, $-CH_2-N-CH_2-$); 3.7–4.1 (m, 4H, $-CH_2-O-CH_2-$); 5.23 (s, 2H, CH_2); 6.66 (s, 1H, H-2); 6.96–7.45 (m, 3H, H-5, H-6, H-7); 7.45–7.83 (m, 1H, H-4)
e	O—CH_2—O		H	C_2H_5	O	$(C_2H_5)_2O$	50	134° (C_2H_5OH)	$C_{15}H_{18}N_2O_3$ (274.3)	1.36 (t, 3H, CH_3); 2.83–3.16 (m, 4H, CH_2-N-CH_2); 3.66–4.2 (m, 6H, $-CH_2-O-CH_2-$, CH_2CH_3); 5.9 (s, 2H, O—CH_2—O); 6.53 (s, 1H, H-2); 6.76, 7.0 (2s, H-4, H-7)
f	F	H	H	C_2H_5	O	$(C_2H_5)_2O$	60	83° [$(i\text{-}C_3H_7)_2O$]	$C_{14}H_{17}FN_2O$ (248.3)	1.4 (t, 3H, CH_3); 2.86–3.26 (m, 4H, CH_2-N-CH_2); 3.76–4.36 (m, 6H, CH_2-O-CH_2, CH_2CH_3); 6.73 (s, 1H, H-2); 6.9–7.46 (m, 3H, H-4, H-6, H-7
g	H	CF_3	H	C_2H_5	O	C_6H_6/C_2H_5OAc, 80:20	52	96° [$(i\text{-}C_3H_7)_2O$]	$C_{15}H_{17}F_3N_2O$ (298.3)	1.32 (t, 3H, CH_3); 2.9–3.15 (m, 4H, CH_2-N-CH_2); 3.7–4.3 (m, 6H, CH_2-O-CH_2, CH_2CH_3); 6.7 (s, 1H, H-2); 7.23 (d, 1H, H-5); 7.70 (m, 2H, H-4, H-7)
h	F	H	F	C_2H_5	O	$(C_2H_5)_2O$	55	108° [$(i\text{-}C_3H_7)_2O$]	$C_{14}H_{16}F_2N_2O$ (266.3)	1.36 (t, 3H, CH_3); 3.0 (t, 4H, CH_2-N-CH_2); 3.9 (t, 4H, CH_2-O-CH_2); 4.2 (q, 2H, CH_2CH_3); 6.72 (s, 1H, H-2); 6.72 (2t, 1H, H-6, J_{HF} = 11 Hz, $J_{H\text{-}6,H\text{-}4}$ = 2 Hz); 7.07 (2d, 1H, H-4, J_{HF} = 10 Hz, $J_{H\text{-}4,H\text{-}6}$ = 2Hz)
i	H	H	H	CH_3	N—CH_3	THF	49	121° [$(i\text{-}C_3H_7)_2O$]	$C_{14}H_{19}N_3$ (229.3)	2.35 (s, 3H, N—CH_3); 2.6 (t, 4H, CH_2-N-CH_2); 3.1 (t, 4H, CH_2-N-CH_2); 3.65 (s, 3H, N—CH_3); 6.57 (s, 1H, H-2); 6.87–7.33 (m, $3H_{arom}$); 7.43–7.83 (m, $1H_{arom}$)

Yield of isolated product based on **4**.
Uncorrected.
The microanalyses were in good agreement with the calculated values (C ±0.22, H ±0.19, N ±0.10).
Recorded at 60 MHz on a Varian A 360 spectrometer.

3-Morpholinoindole (8):
To a stirred solution of sodium (313 mg, 13.6 mmol) in liquid ammonia (80 ml) cooled at −60°, a solution of indole **6d** (2 g, 6.8 mmol) in tetrahydrofuran (10 ml) is added dropwise. At the end of the dropping the reaction is complete, methanol (2 ml) is added, then ammonia is evaporated on a warm water bath (~35–40°). The reaction residue is washed with water and extracted with dichloromethane. The organic layer is dried with anhydrous sodium sulphate and the solvent removed under reduced pressure. The crude residue is purified by column chromatography on silica gel (ratio silica gel/crude product 40:1) and eluted with benzene/ethyl acetate 1:1; yield: 1.1 g (80%); m.p. 143° (from diisopropyl ether).

$C_{12}H_{14}N_2O$	calc.	C 71.26	H 6.98	N 13.85
(202.3)	found	71.2	6.9	13.8

^{1}H-N.M.R. ($CDCl_3$): δ = 3.07 (t, 4H, CH_2-N-CH_2); 3.93 (t, 4H, CH_2-O-CH_2); 6.67 (d, 1H, H-2, $J_{H\text{-}1,H\text{-}2}$ = 2 Hz); 6.83–7.40 (m, $3H_{arom}$); 7.47–8.20 ppm (m, 2H, $1H_{arom}$, NH exch.).

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