Amidomethylation of Indoles and Cyclisations to Spiro[pyrrolo[4,3,2-*de*]isoquinoline-3,4′-piperidines]

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4-Aminomethylindoles react with aldehydes and ketones to form pyrrolo[4,3,2-*de*]isoquinolines. The structures of starting materials and end products were determined using 1D and 2D ^{1}H nmr techniques.

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Discussion.

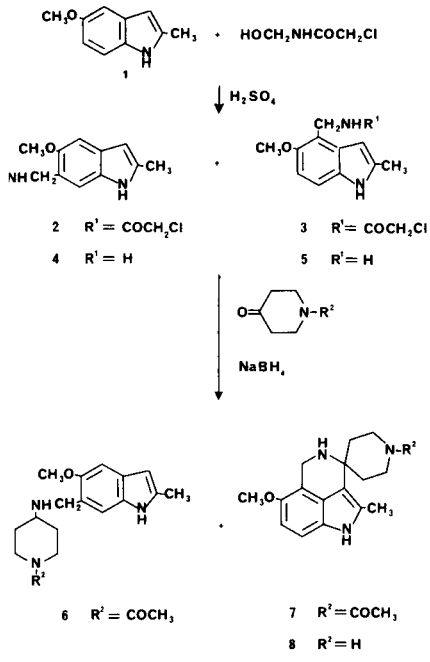
Indoles with annelations involving the 1,2- or 2,3-positions are found frequently in nature [1]. In contrast, indoles with a 3,4-bridge are not very common, with the exception, for example, of the ergot alkaloids and dihydrobufotenin. This may be related to the low reactivity of the 4 position, which is not easily accessible synthetically and which is rarely found substituted in natural products, an exception being psilocibin. In this paper, we present the synthesis and ^{1}H nmr structure elucidation of several 3,4-annelated indole derivatives which were discovered during the preparation of aminomethylindoles.

4-Aminomethylindoles, which are suitable precursors for the synthesis of pyrrolo[4,3,2-*de*]isoquinolines, are accessible from 4-cyanoindoles [2], by rearrangement/reduction of 5-nitroisoquinolinium salts [3], and by direct amidomethylation (Tscherniak-Einhorn Reaction) of 2,5-disubstituted indoles [4]. The latter approach with 2-methyl-5-methoxyindole (**1**) (Scheme 1) proceeds to a mixture of 6 and 4 substituted products **2** and **3** (ratio 9:1), which are difficult to separate due to their very similar chromatographic properties. However, **2** and **3**, as well as **4** and **5** (the corresponding saponification products) were separated in sufficient quantities for ^{1}H nmr structure elucidation.

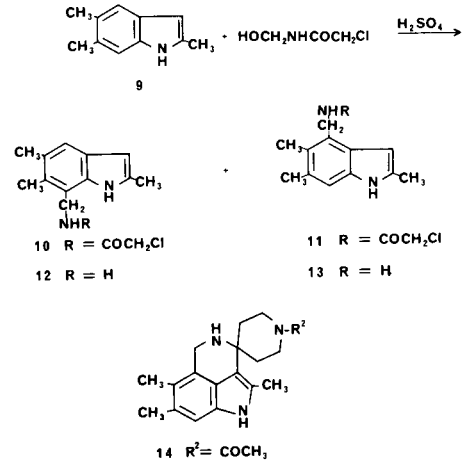
We found that reductive alkylation of the **4**, **5** mixture results in the expected 6-(4-piperidylaminomethy)indole derivative **6** and the unexpected spiro product **7**, two entirely different compounds, which were easily separated by liquid chromatography.

Upon discovery of a 3,4 annelated product, we investigated options to improve the yield of a 4-aminomethyl precursor. Changing the reaction conditions did not significantly improve selectivity for substitution at positions 4 or 6 on the indole ring and still yielded a high **2:3** ratio. Subjecting 2,5,6-trimethylindole (**9**) (Scheme 2) to the Tscherniak-Einhorn conditions produced a small amount of a 4-substituted product **11** while 7-substitution predominated **10**. Nevertheless, we were able to prepare enough 4-aminomethyl-2,5,6-trimethylindole (**13**) to confirm the observations made in the methoxy series and to obtain the corresponding pyrrolo[4,3,2-*de*]isoquinoline (**14**).

Scheme 1



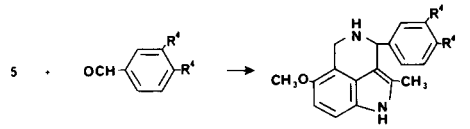
Scheme 2



The spirobisamine **8** was easily prepared by saponification of **7** with potassium hydroxide. It did not possess any interesting biological activity.

Additionally we reacted **5** with benzaldehyde and vanillin (Scheme 3) to produce **15** and **16** respectively. Analogous reactions in the methylaminomethyl series have been recently reported by M. Somei *et al.* [3].

Scheme 3



15 R' = H

16 R' = p-OH, m-OCH_3

Structure Elucidation.

Shown in Table 1 are ^1H nmr assignments for the compounds in the 2-methyl-5-methoxyindole series **1**...**8**. The nmr parameters are consistent with the structures shown in Scheme 1. The position of aminomethyl substitution was confirmed by measurement of J coupling constants between the 4, 6, and 7 protons and by 1D NOE (Nuclear Overhauser Effect) [5] and 2D NOE [6,7] measurements. Ring closure in **7** was evidenced in the ^1H nmr spectrum by the lack of an H(3) resonance. Detailed analysis of the spiro compound **14** (below) allowed confirmation of the structure of **7** by analogy.

The ^1H nmr assignments for the 2,5,6-trimethylindole series **9**...**14** are shown in Table 2. Since there is no observable J coupling in the aromatic resonances of this series, we used 1D and 2D NOE measurements to arrive at unambiguous assignments and to determine the positions of substitution. In **9**, NOE's between H(3) and H(4) on the one hand and between H(7) and the indole N*H* on the other allowed assignment of these resonances and simultaneously confirmed the structure of **9**.

Table 1

^1H NMR Chemical Shifts [a] of 2-Methyl-5-methoxyindole Series

^1H	1	2	3	4	5	6	7	8 [b]
1	10.69	10.75	10.78	10.64	10.71	10.61	10.25	11.07
3	6.02	6.07	6.08	5.99	6.16	6.01	– –	– –
4	6.89	7.10 [c] or 6.98	– –	7.16 or 6.87	– –	7.20 or 6.89	– –	– –
6	6.61	– –	7.17 or 6.79	– –	7.08 or 6.74	– –	6.94 or 6.66	7.19 or 6.88
7	7.13	6.98 or 7.10	6.79 or 7.17	6.87 or 7.16	6.74 or 7.08	6.89 or 7.20	6.66 or 6.94	6.88 or 7.19
2-CH_3	2.34	2.38	2.36	2.49	2.35	2.33	2.34	2.52
5-OCH_3	3.71	3.80	3.79	3.75	3.76	3.75	3.73	3.80
4-CH_2N	– –	– –	4.48	– –	3.82	– –	3.86	4.38
6-CH_2N	– –	4.34	– –	3.70	– –	3.75	– –	– –
4-CH_2Cl	– –	– –	4.04	– –	– –	– –	– –	– –
6-CH_2Cl	– –	4.15	– –	– –	– –	– –	– –	– –
4-CH_2N*H*	– –	– –	8.21	– –	– –	– –	[d]	– –
6-CH_2N*H*	– –	8.50	– –	– –	– –	[d]	– –	– –
4-CH_2NH_2	– –	– –	– –	– –	1.48	– –	– –	– –
6-CH_2NH_2	– –	– –	– –	1.80	– –	– –	– –	– –
2', 6'	– –	– –	– –	– –	– –	2.67 3.01 3.75 4.12	3.02 3.57 4.24	3.30 3.80
3', 5'	– –	– –	– –	– –	– –	1.22 1.79	1.71 1.86	2.29 2.66
4'	– –	– –	– –	– –	– –	2.58	– –	– –
COCH_3	– –	– –	– –	– –	– –	1.96	2.02	– –
NH_2	– –	– –	– –	– –	– –	– –	– –	10.16 [e] 9.27 or 9.86

[a] In ppm relative to TMS at 0.0 ppm. [b] HCl salt. [c] More than one entry indicates either that assignment was not critical for structure elucidation or that broadness or overlap precluded assignment. [d] Not detected due to broadness. [e] These peaks account for both NH_2^+ moieties.

Table 2

^{1}H NMR Chemical Shifts [a] of 2, 5, 6-Trimethylindole Series

^{1}H	9	10	11	12 [b]	13	14
1	10.55	10.60	10.66	11.25	10.57	10.18
3	5.94	6.00	6.10	6.04	6.10	– –
4	7.16	7.16	– –	7.25	– –	– –
7	7.03	– –	7.03	– –	6.96	6.82
2-C*H*$_3$	2.33	2.37	2.19 [c]	2.28	2.23	2.03
			2.29	2.30	2.28	2.10
			or	or	or	2.27
			2.33	2.40	2.35	or
						2.34
5-C*H*$_3$	2.23	2.26	2.19	2.28	2.23	2.03
			2.29	2.30	2.28	2.10
			or	or	or	2.27
			2.33	2.40	2.35	or
						2.34
6-C*H*$_3$	2.25	2.21	2.19	2.28	2.23	2.03
			2.29	2.30	2.28	2.10
			or	or	or	2.27
			2.33	2.40	2.35	or
						2.34
4-C*H*$_2$N	– –	– –	4.50	– –	3.89	3.89
7-C*H*$_2$N	– –	4.57	– –	4.32	– –	– –
4-C*H*$_2$Cl	– –	– –	4.02	– –	– –	– –
7-C*H*$_2$Cl	– –	4.05	– –	– –	– –	– –
4-CH$_2$N*H*	– –	– –	8.27	– –	– –	1.34
7-CH$_2$N*H*	– –	8.43	– –	– –	– –	– –
4-CH$_2$N*H*$_2$	– –	– –	– –	– –	1.65	– –
7-CH$_2$N*H*$_2$	– –	– –	– –	– –	– –	– –
CO*CH*$_3$	– –	– –	– –	– –	– –	2.03
						2.10
						2.27
						or
						2.34
2′, 6′	– –	– –	– –	– –	– –	3.04
						3.60
						4.27
3′, 5′	– –	– –	– –	– –	– –	1.70
						1.88
N*H*$_3^+$	– –	– –	– –	8.34	– –	– –

[a] In ppm relative to TMS at 0.0 ppm. [b] HCl salt. [c] More than one entry indicates either that assignment was not critical for structure elucidation or that broadness or overlap precluded assignment.

The chemical shifts of H(4) and H(7) are very similar; therefore, we were reluctant to use these values to determine the position of amidomethylation in **10** and **11**. 2D NOE measurements, however, (shown for **11** in Figure 1) could be used to determine this definitively. The normal spectrum is visualized along the diagonal (lower left to upper right) and off-diagonal peaks (cross-peaks) indicate NOE's and therefore reflect spatial proximity between nuclei. For example, the indole N*H* exhibits cross-peaks with H(7) and C*H*$_3$(2), allowing unambiguous assignment of these peaks. All peaks in this spectrum can be assigned following this approach. Spectra of **12** and **13** can be assigned by analogy with **10** and **11** respectively.

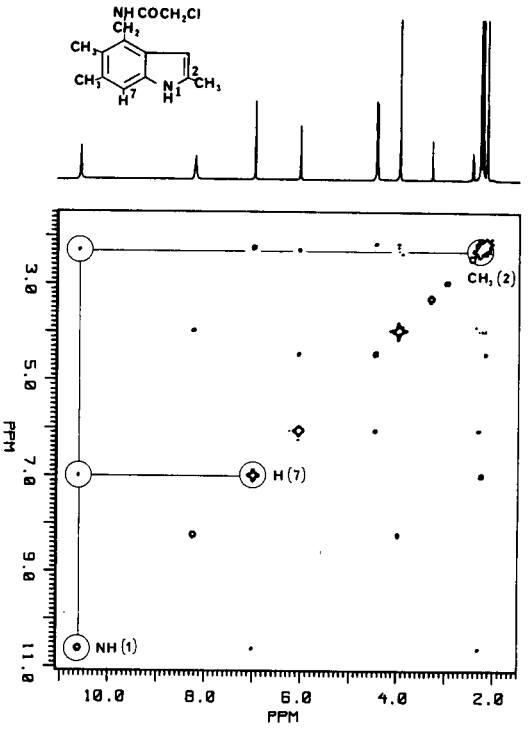


Figure 1 ^{1}H 2D NOE spectrum of **11**.

Ring closure in **14** is confirmed by the absence of an H(3) resonance. Since **14** was an unexpected product, we utilized several nmr techniques to provide complementary structural data. To prove that the carbon attached to C(3) was, in fact, a quaternary carbon, we obtained a 2D J-resolved spectrum [8] (Figure 2). The two axial piperidine hydrogens which are α to this carbon each exhibit only two large (*ca.* 12 Hz) coupling constants (J geminal and J vicinal-axial-axial). If the carbon in question bore a

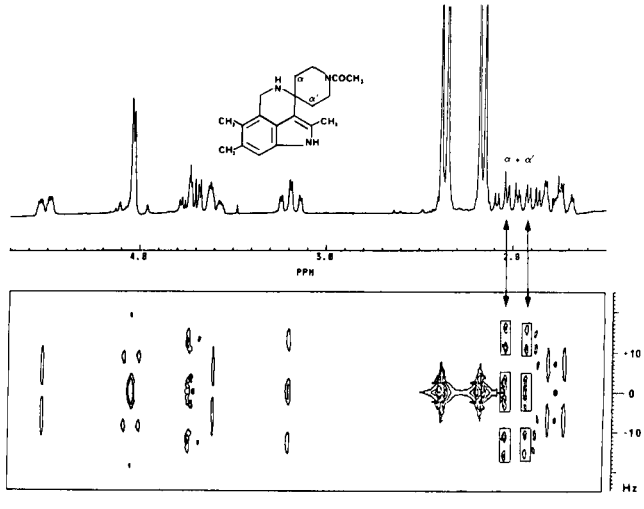


Figure 2 ^{1}H 2D J-resolved spectrum of **14**.

hydrogen as a result of annelation involving the aminomethyl nitrogen, then three large couplings would be observed. The ^{13}C nmr spectra (^{1}H broad-band decoupled and INEPT [9]) support this conclusion by revealing a quaternary carbon (the spiro carbon).

In Table 3 the assignments for the benzaldehyde-vanillin series are shown. The assignments were determined using the techniques already mentioned and are consistent with structures **5**, **15** and **16**.

Table 3

^{1}H NMR Chemical Shifts [a] of Benzaldehyde and Vanillin Series

^{1}H	5	15	16
1	10.71	10.35	10.29
3	6.16	– –	– –
6	7.08 [b]	6.69	6.69
	or	or	or
	6.74	7.00	6.98
7	6.74	7.00	6.98
	or	or	or
	7.08	6.69	6.69
2-CH_3	2.35	1.92	1.92
3-CH	– –	5.07	4.95
5-OCH_3	3.76	3.75	3.70
			or
			3.72
4-CH_2N	3.82	3.83	3.87
4-CH$_2$NH	– –	2.68	3.00 [c]
4-CH$_2$NH_2	1.48	– –	– –
phenyl	– –	7.28	– –
2′	– –	– –	6.93
5′	– –	– –	6.69
6′	– –	– –	6.61
3′-OCH_3	– –	– –	3.72
			or
			3.70
4′-OH	– –	– –	8.83 [c]

[a] In ppm relative to TMS at 0.0 ppm. [b] More than one entry indicates either that assignment was not critical for structure elucidation or that broadness or overlap precluded assignment. [c] Very broad resonance.

Utilizing ^{1}H nmr we have analyzed the structure of products resulting from condensation of 4-aminomethylindoles with 4-piperidone, benzaldehyde and vanillin. Notably, 3,4-annelated compounds **7**, **14**, **15** and **16** were found along with the expected reaction products. This discovery provides new avenues to these annelated indoles, compounds which otherwise are difficult to synthesize.

EXPERIMENTAL

The ^{1}H (270 MHz, 250 MHz) and ^{13}C (67.9 MHz) nmr spectra were obtained with an IBM Instruments NR270-AF Spectrometer or with a Bruker WM250 Spectrometer, operating in the pulse-Fourier transform mode. Pulse sequences employed were obtained from the literature cited above or from the manuals supplied by IBM Instruments and Bruker. Melting points were determined with a Buchi 510 melting point apparatus and are uncorrected. Elemental analyses were carried out by Micro-Tech Laboratories, Skokie, Illinois. Preparative high performance liquid chromatography was performed with a Waters Prep 500 instrument.

1-Acetyl-6-methoxy-2-methyl-1,3,4,5-tetrahydrospiro[pyrrolo[4,3,2-*de*]isoquinoline-3,4′-piperidine] (**7**).

A mixture of 31.0 g (116 mmoles) of 6- and 4-chloroacetamidomethyl-5-methoxy-2-methylindoles (**2** and **3**) [4] and 13.0 g (232 mmoles) of potassium hydroxide was heated to reflux in 600 ml of ethanol for 20 hours. The solution was concentrated under vacuum, poured into ice/water and extracted with dichloromethane (3 x 300 ml). The combined and dried extracts were evaporated to dryness and the residue, 15.8 g, 72%, consisting of a mixture of 6- and 4-aminomethyl-5-methoxy-2-methylindoles, was used for the next step.

The above residue, 15.7 g (82 mmoles) and 11.7 g (83 mmoles) *N*-acetyl-4-piperidone, were heated to reflux in 400 ml of ethanol for 22 hours under nitrogen. The solution was cooled in an ice bath, then 61.0 g (166 mmoles) of sodium borohydride was added and the mixture was allowed to stir under nitrogen for 20 hours. After decomposition with ice/water, the reaction products were extracted with ethyl acetate (3 x 200 ml), the combined extracts were washed, dried and evaporated to dryness. The residue was applied to a silica gel column (25 cm, 10 cm diameter) and eluted with dichloromethane/methanol, starting with a ratio 97:3 and ending with 90:10. The material eluted with the first fraction (tlc on silica, 90/10 dichloromethane/methanol, Rf 0.7) was crystallized from ethanol to give 2.1 g, 8.2% of compound **7**, mp 245-247°.

Anal. Calcd. for $C_{18}H_{23}N_3O_2$: C, 68.98; H, 7.40; N, 13.41. Found: C, 68.70; H, 7.69; N, 13.21.

6-(1-Acetyl-4-piperidylaminomethyl)-5-methoxy-2-methylindole (**6**).

The next major fraction eluted from the above column, (tlc Rf 0.2) was crystallized from ethyl acetate, 5.2 g, 20%, mp 108-113°.

Anal. Calcd. for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.11. Found: C, 68.61; H, 8.06; N, 13.36.

6-Methoxy-2-methyl-1,3,4,5-tetrahydrospiro[pyrrolo[4,3,2-*de*]isoquinoline-3,4′-piperidine] (**8**).

The amide **7** (1.4 g, 4 mmoles) was heated to reflux in 50 ml of ethanol with 0.9 g (16 mmoles) of potassium hydroxide for 48 hours. The solution was concentrated to a small volume *in vacuo* and poured into ice/water. The residue from dichloromethane extraction was converted to the hydrochloride with ethereal hydrogen chloride and recrystallized from ethanol, 0.6 g, 39%, mp >220°.

Anal. Calcd. for $C_{16}H_{21}N_3O{\cdot}2HCl$: C, 55.80; H, 6.73; N, 12.21. Found: C, 56.20; H, 6.93; N, 12.30.

7-Chloroacetamidomethyl-2,5,6-trimethylindole (**10**).

Concentrated sulfuric acid (75 ml) was cooled to below 5°. 2,5,6-Trimethylindole (**9**) (11.6 g, 73 mmoles) [10] was added slowly under stirring and cooling; stirring was continued until all indole was dissolved. Then *N*-hydroxymethylchloroacetamide (9.0 g, 73 mmoles [11]) was added slowly and the mixture stirred for 16 hours at 5°. The viscous solution was poured on ice, neutralized with ammonia and extracted with dichloromethane (3 x 400 ml). The combined extracts were washed with sodium bicarbonate solution, dried and evaporated to dryness. The beige, amorphous solid was not completely dried; it was stored at 5° and protected from light until used for chromatographic separation. Tlc on silica (dichloromethane, 2% ethyl acetate) showed two major components with Rf 0.3 and 0.2. Preparative hplc was carried out with the same solvent mixture in several runs, due to the low solubility of the crude reaction product.

The fraction eluting first, 9.1 g, 47%, mp 187-189° (from ethanol), was compound **10**.

Anal. Calcd. for $C_{14}H_{17}ClN_2O$: C, 63.51; H, 6.47; Cl, 13.39; N, 10.58. Found: C, 63.15; H, 6.45; Cl, 13.89; N, 10.38.

4-Chloroacetamidomethyl-2,5,6-trimethylindole (**11**).

The fraction eluting second from the column in the above separation was crystallized from ethanol, 5.2 g, 27%, mp 196-198°.

Anal. Calcd. for $C_{14}H_{17}ClN_2O$: C, 63.51; H, 6.47; Cl, 13.39; N, 10.58. Found: C, 63.50; H, 6.57; Cl, 13.34; N, 10.27.

7-Aminomethyl-2,5,6-trimethylindole (**12**).

A mixture of **10** (4.5 g, 17 mmoles), potassium hydroxide (2.4 g, 40 mmoles) and 125 ml of ethanol was heated to reflux for 16 hours. The solvent was removed *in vacuo*, water was added and the mixture was extracted with dichloromethane (3 x 200 ml). The residue from evaporation of the combined and dried extracts was converted to the hydrochloride and recrystallized from ethanol, 2.3 g, 63%, mp dec >200°.

Anal. Calcd. for $C_{12}N_{16}N_2 \cdot HCl$: C, 64.13; H, 7.62; N, 12.47; Cl, 15.78. Found: C, 63.92; H, 7.84; N, 12.11; Cl, 15.27.

4-Aminomethyl-2,5,6-trimethylindole (**13**).

The chloroacetyl compound **11** was saponified as described above. The crude product was recrystallized as the free base from ethanol, 60%, mp 158-160°. No satisfactory elemental analysis was obtained ($C_{12}H_{16}N_2$) because of instability to air and light. The product was used as such for the subsequent step.

1'-Acetyl-2,6,7-trimethyl-1,3,4,5-tetrahydrospiro[pyrrolo[4,3,2-*de*]isoquinoline-3,4'-piperidine] (**14**).

A mixture of **13** (1.0 g, 5.3 mmoles), *N*-acetyl-4-piperidone (0.8 g, 5.3 mmoles) and ethanol (40 ml) was heated to reflux for 16 hours. The solution was poured on ice and extracted with ethyl acetate (2 x 200 ml). The residue, after drying and evaporation, was crystallized from ethyl acetate, 1.3 g, 79%, mp 240-244°.

Anal. Calcd. for $C_{19}H_{25}N_3O$: C, 73.28; H, 8.09; N, 13.49. Found: C, 73.31; H, 8.18; N, 13.02.

3-Phenyl-6-methoxy-2-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinoline (**15**).

A solution of 4-aminomethyl-5-methoxy-2-methylindole [4] (**5**) (1.4 g, 7.4 mmoles) and benzaldehyde (0.9 g, 8.0 mmoles) in 50 ml of ethanol was heated to reflux for 24 hours. The residue after evaporation was crystallized from dimethylformamide, 1.3 g, 64%, mp 209-222°.

Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.07. Found: C, 77.81; H, 6.81; N, 10.20.

3-(4-Hydroxy-3-methoxyphenyl)-6-methoxy-2-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinoline (**16**).

This compound was prepared from **5** and vanilline as described for **15**. 15% yield, mp 204-207° (from ethanol).

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.22; N, 8.64. Found: C, 69.87; H, 6.25; N, 8.55.

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