Regioselective Methylation of 7,12-Dihydropyrido[3,2-*b*:5,4-*b*']diindole. Experimental and Computational Results

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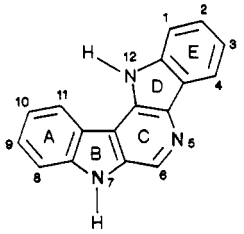
The heterocyclic base, 7,12-dihydropyrido[3,2-*b*:5,4-*b*']diindole 1, was first reported in 1985.[1] It was later discovered that 1 possesses high affinity for the benzodiazepine receptor in vitro and exhibits a broad range of pharmacological profiles when the E ring of the heterocycle is substituted with various functional groups.[2] The pyridodiindoles are the first completely rigid planar benzodiazepine receptor ligands to have been prepared and provide a powerful tool with which to probe the topography of these receptors.[2]

It was of interest to determine the role of the indole NH functionality at N(7) and N(12) of 1 with regard to benzodiazepine receptor affinity. In analogy to results in the β-carboline area, methylation of the indole nitrogens of 1 should prevent ligand–receptor hydrogen-bonding interactions[3] at N(7)H and/or N(12)H with benzodiazepine receptors. The task at hand was to differentiate between the nearly identical indole nitrogens N(7) and N(12) of 1 and permit a regioselective synthesis of each monomethylpyridodiindole, as well as a synthesis of the corresponding 7,12-dimethylpyridodiindole.



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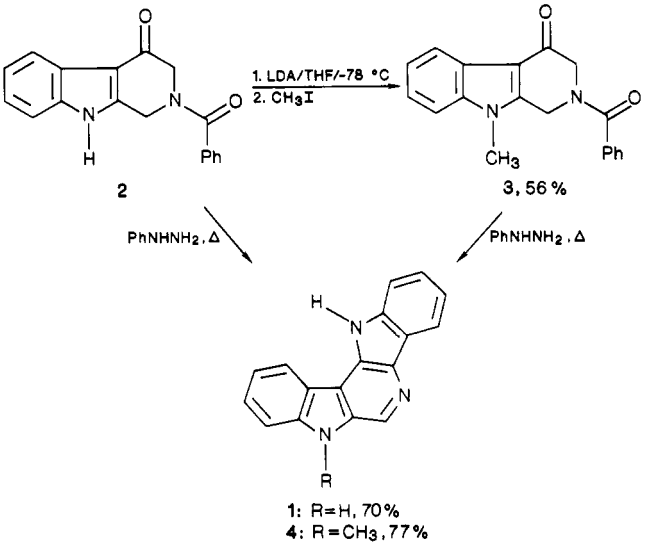
Results and Discussion

The dihydropyridodiindole 1 was originally prepared via the Fischer indole cyclization by heating 2-benzoyl-4-oxotetrahydronorharmane **2**[1,4] and neat phenylhydrazine at 200 °C (70% yield).[1] The synthesis of the 7-methylpyridodiindole 4 was effected in similar fashion by utilization of N_a-methyl-2-benzoyl-4-oxotetrahydronorharmane (**3**) in a Fischer indole cyclization reaction (Scheme I). The N_a-methyl analogue 3 was prepared in 56% yield from 2 as illustrated in Scheme I, and was then heated in neat phenylhydrazine at 150 °C for 7 h. Anhydrous hydrazine was then added, and the mixture was heated at reflux for 16 h to provide 4 in 77% yield (Scheme I).

The synthesis of the 12-methyl regioisomer, **5**, was less straightforward since it was known from previous work that phenylhydrazones of 2 substituted with deactivating groups readily disproportionate in acidic media to yield

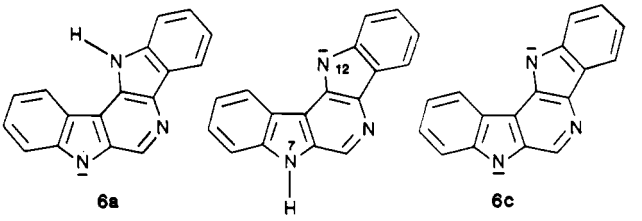
Scheme I



2 3, 56%

1: R=H, 70%
4: R=CH3, 77%

Table I. Net Charge Densities of N(7) and N(12) in 1 and 6a–c



6a 6b 6c

compd	N(7)	N(12)	relative stability, kcal/mol
1	−0.248	−0.252	
6a	−0.337	−0.260	0
6b	−0.263	−0.354	3.33
6c	−0.383	−0.379	37.95

4-amino-β-carbolines.[5] Simple alkylations of 1 were expected to give mixtures of mono- and dimethylated diindoles since there was no obvious reason to believe that N(7) would react differently than N(12) with electrophilic reagents (see 1). To probe the existence of subtle inherent quantitative differences in the reactivity of N(7) and N(12), which could be exploited synthetically to provide **5** regioselectively, we investigated the electron density distributions and thermodynamic stabilities of the intermediate anions.

The net atomic charge densities of N(7) and N(12) were calculated for geometry optimized structures of 1 and **6a–c** (R = H) by using MNDO.[6] The net charge densities of N(7) and N(12) for compounds 1 and **6a–c** are listed in Table I. From comparison of the net charge density on N(7) with that on N(12) in either the parent compound 1 or the dianion **6c**, it it clear there is little difference in the electron density present on N(7) and N(12). On the basis of these data alone, an electrophilic methylating reagnet would probably not differentiate between the two indolic nitrogen atoms of 1 or dianion **6c**, and consequently a mixture of methylated diindoles would be anticipated. However,

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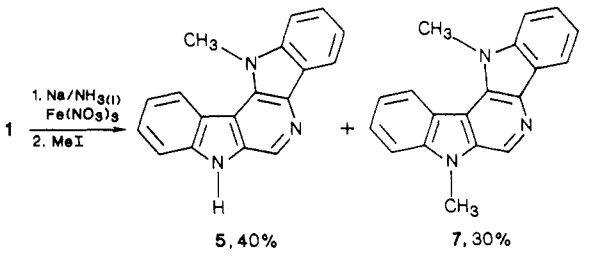
(3) For a proposed model of the benzodiazepine receptor pharmacophore, see: Allen, M.; Hagen, T. J.; Trudell, M. L.; Codding, P. W.; Skolnick, P.; Cook, J. M. *J. Med. Chem.*, in press.
(4) Cain, M.; Mantei, R.; Cook, J. M. *J. Org. Chem.* **1982**, *47*, 4933–4936.
(5) Trudell, M. L.; Fukada, N.; Cook, J. M. *J. Org. Chem.* **1987**, *52*, 4293–4296.
(6) (a) Dewar, M. J. S.; Theil, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899–4907. (b) The QCPE program was expanded to 50-atom capability by Sorenson, T.; England, W. B., unpublished results.

0022-3263/88/1953-4873$01.50/0

Scheme II



calculations for the monoanions **6a** and **6b** indicate that substantial differences in the charge density at the anionic sites versus the charge density at the NH sites exist (Table I).

To predict which monoanion would form preferentially, the relative thermodynamic stabilities of the intermediate monoanions **6a** and **6b**, as well as the dianion **6c**, were calculated from geometry-optimized structures with MNDO.[6] The relative stabilities calculated for **6a–c** are listed in Table I. The calculated data suggest that the anion formed at N(7), **6a**, is more stable than the anion formed at N(12), **6b**, by 3.33 kcal/mol. From these data it was predicted that the monoanion **6a** could be generated regioselectively under thermodynamic conditions and then methylated to provide **4**. In order to verify this hypothesis and evaluate the MNDO data, **1** was treated with potassium hydride (KH, 1 equiv) in dimethyl sulfoxide (DMSO). The reaction mixture was then stirred at 25 °C to permit equilibration between the dimsyl anion and the thermodynamically more stable monoanion **6a**. After 15 min, methyl iodide (1 equiv) was added. Workup gave the monomethyl derivative **4** regioselectively in 71% yield, which confirmed the prediction based on the MNDO data.

Although the net charge densities on N(7) and N(12) of **6c** are almost identical, on the basis of the thermodynamic data obtained for anions **6a** and **6b**, it was predicted that regioselective methylation of N(12) was possible. It was felt that upon generation of the dianion **6c** followed by the addition of 1 equiv of methyl iodide, methylation of N(12) would occur regioselectively to provide the more thermodynamically stable monoanion (**6a**; $N(12)CH_3$). Moreover, approach of an incoming electrophile at N(7) is hindered to a greater degree by protons H(6) and H(8) (interatomic distance: N(7)–H(6) = N(7)–H(8) = 2.88 Å), than N(12) is hindered by H(1) and H(11) (interatomic distance: N(12)–H(1) = 2.90 Å; N(12)–H(11) = 3.45 Å). Since an approaching electrophile should favor reaction at N(12), quenching the monoanion that results with water should provide **5**, regioselectively. The synthesis of **5** was attempted by employing standard conditions for the methylation of indoles.[7] The pyridodiindole **1** was treated with excess sodium (Na, 2.5 equiv) in liquid ammonia [$Fe(NO_3)_3$ was added in a catalytic amount to favor the formation of $NaNH_2$],[8] followed by the addition of methyl iodide (1.5 equiv). Upon workup, 12-methylpyridodiindole (**5**) was isolated as the major product in 40% yield (Scheme II). The 7,12-dimethylpyridodiindole **7** was also formed in this reaction. The dimethyldiindole **7** was obtained as the hydrochloride salt in 30% yield (Scheme II). The two compounds were easily separated as their HCl salts by crystallization. None of the monomethyl derivative **4** was observed under these conditions, which implies that methylation of N(12) of **6c** occurs regioselectively, where **7** probably results from methylation of **5** due to the presence of excess methyl iodide. The structure of **5** was confirmed by ^1H NMR spectroscopy by using NOE difference spectra. Efforts to reduce the formation of **7** and increase the yield of **5** by decreasing the amount of methyl iodide were unsuccessful and resulted in inseparable mixtures of the starting pyridodiindole **1** and 12-methylpyridodiindole (**5**).

To ensure that the ferric salt did not alter the course of the reaction, the methylation reaction was repeated with $Na/NH_3(l)$ in the absence of ferric nitrate. The monoalkylated base 12-methylpyridodiindole (**5**) was isolated as the major product (21% yield), accompanied by only traces of the dimethyl derivative **7** observed by TLC. The low overall yield can be attributed to the reductive nature of the reaction conditions, which, presumably, resulted in decomposition of the pyridodiindole **1**. Isolation of 12-methylpyridodiindole (**5**) reconfirms that methylation of the dianion **6c** at N(12) rather than N(7) occurs regioselectively and is not influenced by the presence of the ferric salt.

In summary, MNDO calculations have provided useful and reliable data in regard to the reactivity of **1**[9] and have been exploited in a regioselective synthesis of the 7- and 12-monomethylpyridodiindoles **4** and **5**. Reaction conditions were developed such that the methylating agent (MeI) effectively differentiated between the chemically similar indolic nitrogen atoms at N(7) and N(12). The ability to regioselectively methylate N(7) under thermodynamic control and N(12) via the dianion **6c** when coupled with previous work[1,9] permits the selective functionalization of **1** at positions 1–4, 7, 10, and 12. This provides a powerful class of compounds with which to probe the topography of the benzodiazepine receptor.[3] The results of this study will be reported elsewhere.

Experimental Section

Microanalyses were performed on a F and M Scientific Corp. Model 185 carbon, hydrogen, and nitrogen analyzer. Melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. Proton NMR spectra were recorded on a Bruker 250-MHz multiple-probe spectrometer. IR spectra were taken on either a Beckman Acculab-1, a Nicolet MX-1, or a Mattson Polaris IR-10400 spectrometer. Low-resolution mass spectral data (EI/CI) were obtained on a Hewlett-Packard 5855 GC–mass spectrometer, while high-resolution mass spectra were taken on a Finnigan HR mass spectrometer. Analytical TLC plates used were E. Merck Brinkmann UV-active silica gel. Unless otherwise stated, all chemicals were purchased from Aldrich Chemical Co.

2-Benzoyl-4-oxo-1,2,3,4-tetrahydro-9-methylpyrido[3,4-*b*]indole (3). To a stirred solution of diisopropylamine (181 mg, 1.80 mmol) in dry THF (20 mL) at 0 °C under N_2 was added a solution of 2.5 M *n*-butyllithium in hexane (0.60 mL, 1.80 mmol). The colorless solution was stirred for 15 min and then cooled to −78 °C. A solution of the ketobenzamide **2** (500 mg, 1.70 mmol) in THF (30 mL) was added dropwise, and the mixture was stirred for 20 min. Methyl iodide (280 mg, 2.0 mmol) was added dropwise, and the reaction mixture was then allowed to warm to room temperature. The reaction mixture was poured into aqueous saturated $NaHCO_3$ (100 mL) and extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine (200 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to provide an oil. The oil was recrystallized from EtOAc to afford **3** (296 mg, 56%): mp >300 °C; IR (KBr) 1650, 1628 cm^{-1}; MS (CI, CH_4), *m/e* 305 (M + 1); ^1H NMR (DMSO-d_6) δ 7.95 (d, *J* = 7.5 Hz, 1 H), 7.63 (d, *J* = 6.3 Hz, 1 H), 7.49 (m, 4 H), 7.30 (m, 3 H), 5.20 (s, 2 H), 4.00 (s, 2 H), 3.40 (s, 3 H). Anal. Calcd for

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$C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 75.02; H, 5.25; N, 9.07.

7-Methyl-12-hydropyrido[3,2-*b*:5,4-*b*']diindole (4). (A) From 3. The β-carboline **3** (100 mg, 0.33 mmol) was added to phenylhydrazine (5 mL), and the mixture was heated at 150 °C for 7 h. The reaction mixture was cooled, anhydrous hydrazine (4 mL) was added and the reaction mixture was refluxed for 16 h. The reaction mixture was then cooled to room temperature, and the yellow precipitate that resulted was collected by vacuum filtration to provide **4** (68 mg; 77% yield): mp >300 °C; MS (CI, CH_4), *m/e* 272 (M + 1); IR (KBr) 3450, 1460, 1325, 730 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.10 (s, 1 H), 9.45 (s, 1 H), 8.97 (d, *J* = 7.9 Hz, 1 H), 8.55 (d, *J* = 7.9 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 7.93 (d, *J* = 8.4 Hz, 1 H), 7.85 (t, *J* = 8.1 Hz, 1 H), 7.65 (t, *J* = 7.2 Hz, 1 H), 7.55 (t, *J* = 7.0 Hz, 1 H), 7.43 (t, *J* = 7.2 Hz, 1 H), 4.20 (s, 3 H). The hydrochloride salt was prepared by adding **4** to a cold saturated solution of methanolic hydrogen chloride. The precipitate that resulted was collected by vacuum filtration to afford **4**·HCl (73 mg, 95%): mp >300 °C. Anal. Calcd for $C_{18}H_{13}N_3$·HCl: C, 70.24; H, 4.38; N, 13.65. Found: C, 69.94; H, 4.48; N, 13.54.

(B) By Methylation of 1. A solution of **1** (100 mg, 0.39 mmol) in DMSO (1 mL) was added to a solution of KH (16 mg, 0.40 mmol) in dry DMSO (1 mL) at 25 °C. The reaction mixture was maintained under an atmosphere of Ar and stirred for 15 min. Methyl iodide (55 mg, 0.44 mmol) was then added directly, and the mixture was stirred for an additional 30 min. The solution was then poured into water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic portions were washed with water (2 × 50 mL) and brine (2 × 50 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to provide an oil. A cold saturated solution of methanolic hydrogen chloride was added. The precipitate that resulted was collected by vacuum filtration to afford **4**·HCl (85 mg, 71%).

7-Hydro-12-methylpyrido[3,2-*b*:5,4-*b*']diindole Hydrochloride (5·HCl). A 250-mL three-neck round-bottom flask equipped with a mechanical stirrer and dry-ice condenser was cooled in a dry ice/acetone bath and filled with liquid ammonia (150 mL). Metallic sodium (115 mg, 5.0 mmol) and a catalytic amount of $Fe(NO_3)_3$·$9H_2O$ were added with stirring. After 1 h, **1** (500 mg, 2 mmol) was added in one portion and the mixture was stirred for 10 min. Methyl iodide (430 mg, 3 mmol) was added dropwise, and the reaction mixture was removed from the cooling bath. The ammonia was allowed to evaporate overnight. The residue that resulted was dissolved in MeOH and added to a solution of saturated methanolic hydrogen chloride. The excess solvent was removed in vacuo to provide a mixture of **5** and **7** as their hydrochloride salts. The solid mixture was dissolved in MeOH/CH_3CN (1:1). Upon standing at room temperature, **5** crystallized as its hydrochloride salt selectively from the mixture. The filtrate was concentrated, and the dimethylpyridodiindole **7** was obtained in pure form as the hydrochloride salt by repeated recrystallizations from MeOH.

7-Hydro-12-methylpyrido[3,2-*b*:5,4-*b*']diindole Hydrochloride (5·HCl) (275 mg; 40%): mp >300 °C; MS (CI, CH_4), *m/e* 272 (M + 1); IR (KBr) 3300, 1450, 1310, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.0 (s, 1 H), 9.15 (s, 1 H), 8.82 (d, *J* = 8.3 Hz, 1 H), 8.62 (d, *J* = 8.2 Hz, 1 H), 7.96 (d, *J* = 7.3 Hz, 1 H), 7.86 (d, *J* = 8.3 Hz, 1 H), 7.75 (t, *J* = 8.0 Hz, 1 H), 7.69 (t, *J* = 7.3 Hz, 1 H), 7.50 (t, *J* = 7.0 Hz, 1 H) 7.42 (t, *J* = 7.3 Hz, 1 H), 4.60 (s, 3 H). Anal. Calcd for $C_{18}H_{13}N_3$·HCl·$^1/_4H_2O$: C, 69.23; H, 4.67; N, 13.46. Found: C, 69.04; H, 4.46; N, 13.08.

7,12-Dimethylpyrido[3,2-*b*:5,4-*b*']diindole Hydrochloride (7·HCl) (190 mg; 30%): mp >300 °C; MS (CI, CH_4), *m/e* 286 (M + 1); IR (KBr) 3400, 1450, 1310, 725 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.45 (s, 1 H), 8.90 (d, *J* = 7.6 Hz, 1 H) 8.60 (d, *J* = 7.5 Hz, 1 H), 8.00 (d, *J* = 7.3 Hz, 1 H), 7.91 (d, *J* = 7.3 Hz, 1 H), 7.85 (t, *J* = 7.5 Hz, 1 H), 7.75 (t, *J* = 7.5 Hz, 1 H), 7.55 (t, *J* = 7.5 Hz, 1 H), 7.45 (t, *J* = 7.5 Hz, 1 H), 4.70 (s, 3 H), 4.20 (s, 3 H). Anal. Calcd for $C_{19}H_{15}N_3$·HCl: C, 70.91; H, 5.01; N, 13.06. Found: C, 71.19; H, 5.04; N, 13.09.

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Registry No. 1, 98263-45-7; 2, 98263-41-3; 3, 116130-38-2; 4, 116130-39-3; 4·HCl, 116130-40-6; 5, 116130-41-7; 5·HCl, 116130-42-8; 6a, 116130-43-9; 6b, 116130-44-0; 6c, 116130-45-1; 7, 116130-46-2; 7·HCl, 116130-47-3; $PhNHNH_2$, 100-63-0.

A Formal Total Synthesis of Kopsinine

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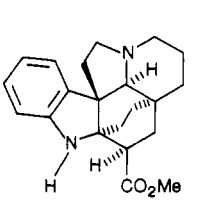
Recently a three-step reaction sequence (Scheme I) was put forward as a facile mode of construction of the pentacyclic nucleus of the Aspidosperma alkaloids.[1] The substitution pattern of the product **1** made the substance ideally suited for conversion into kopsinine (**2**), a hexacyclic indoline alkaloid biosynthetically related to the Aspidosperma alkaloid family. The keto ester **1** required transformation into diene esters **3** on the assumption of the latter being amenable to Diels–Alder chemistry as an approach to the kopsinine skeleton. The functional group manipulation needed for the **1** → **3** transformation is the subject of the present paper.



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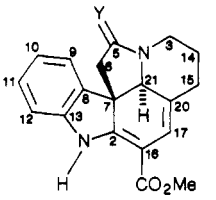

3a: Y = O
b: Y = H_2

The keto ester **1** had been converted earlier into the olefinic ester **5a** by way of sodium borohydride reduction and polyphosphoric acid induced dehydration of the resultant hydroxy ester **4a**.[1] The water extrusion now could be improved by treatment of alcohol **4a** with methanesulfonyl chloride and triethylamine and β-elimination of the resultant mesylate **4b** with potassium hydride. Oxidation of indoline **5a** with lead tetraacetate led to dienamine ester **3a**. An alternate route to the latter involved the lead tetraacetate oxidation of hydroxy ester **4a**. The product mixture consisted of vinylogous urethane **6**, its dehydration product (**3a**), and the aryl acetate **7**. Exposure of alcohol **6** to methanesulfonyl chloride and diisopropylethylamine furnished more dienamine ester **3a**.

The keto ester **1** had been transformed earlier into the hyroxy ester **4c** via diborane reduction of the lactam moiety and subsequent sodium borohydride reduction of the ketone unit.[1] Treatment of alcohol **4c** now with methanesulfonyl chloride and diisopropylethylamine afforded mesylate **4d**, whose solvolysis in acetonitrile led to a mixture of olefinic esters **5b** and **8**, but whose β-elimination with potassium hydride gave exclusively the conjugated olefinic ester **5b**. Lead tetraacetate oxidation of the latter produced dienamine ester **3b**.[2,3] In view of the recent transmutation of this diene ester into (±)-kopsinine

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