On the Mechanism of the Reduction of 1-Phenyl-3-(4-pyridinylmethylene)-2-oxindole with Sodium Borohydride in Methanol

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Sodium borohydride reduction of 1-phenyl-3-(4-pyridinylmethylene)-2-oxindole **1** in methanol gives a high yield of the oxindole **2**, a precursor to linopirdine. The reduction is accelerated by methanol and the major by-products during this reduction are the diastereomeric Michael adducts between **1** and **2** and the overreduced products, **9** and **11**. Surprisingly, indole **9** is not derived from further reduction of **2** but is formed concurrently, whereas the ring opened product **11** is the unexpected reduction product derived from **2**.

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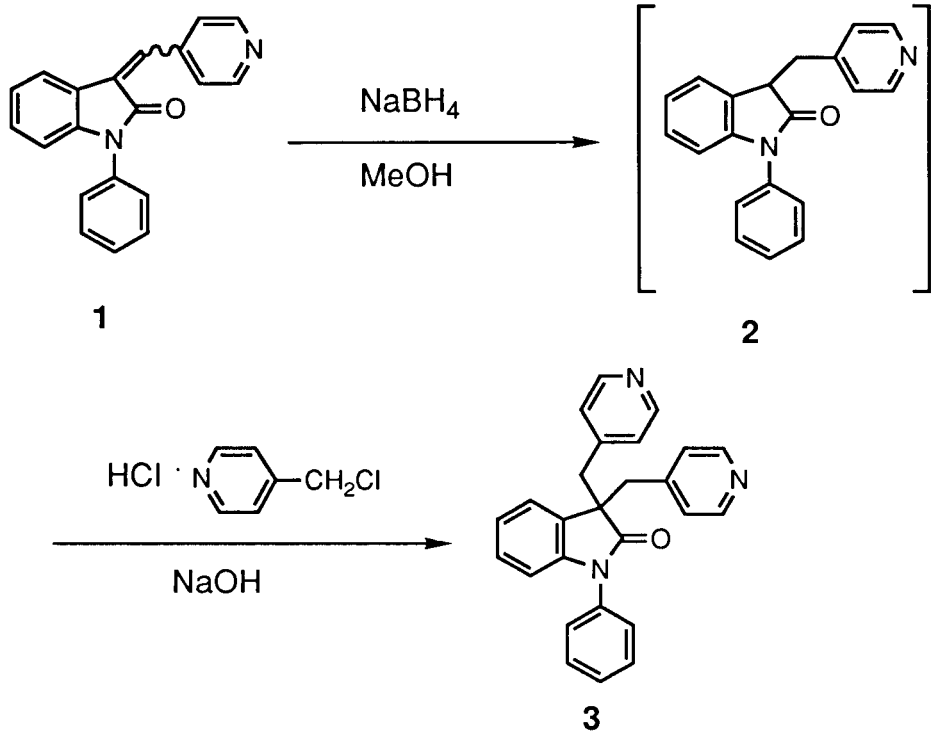
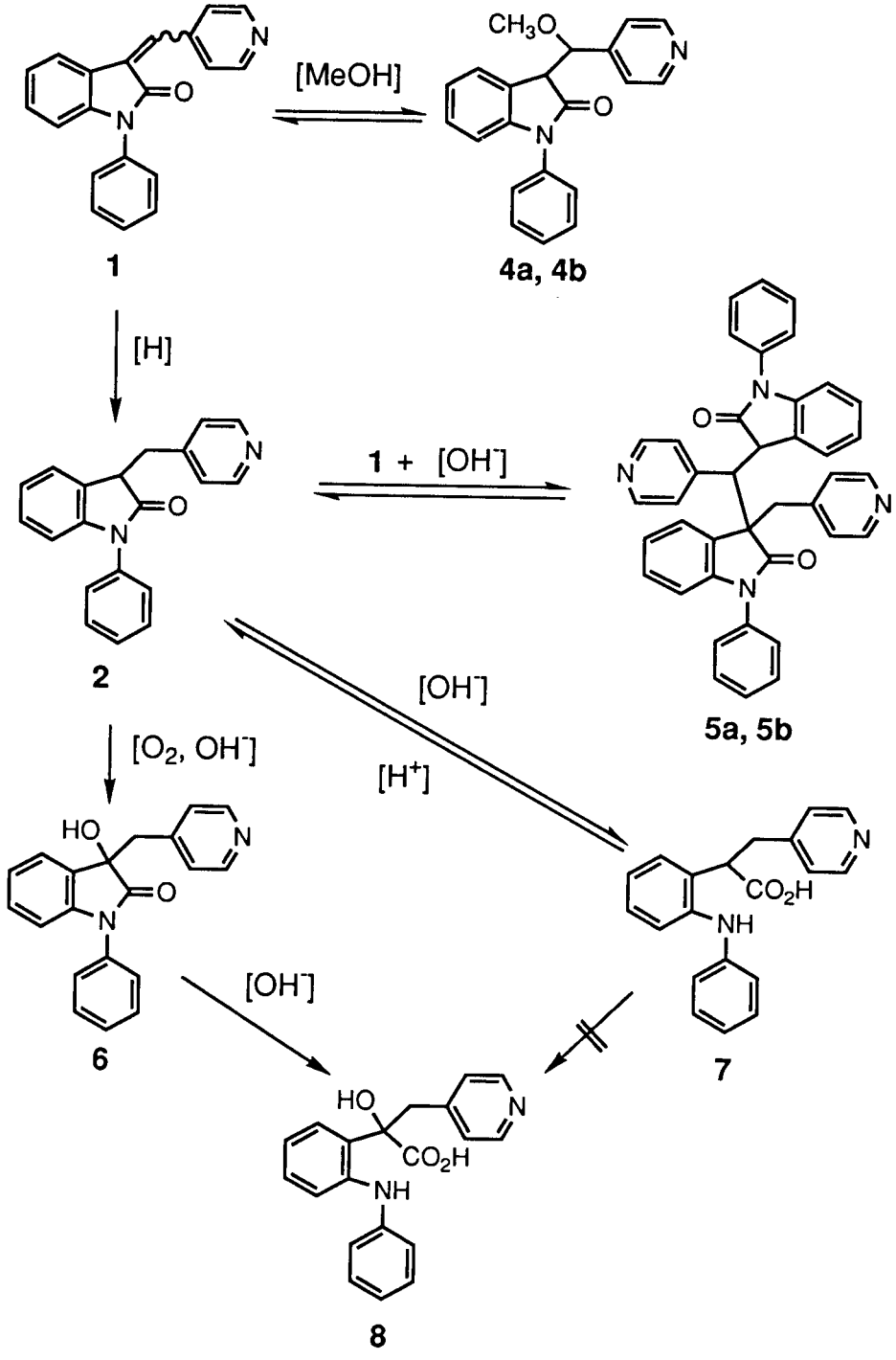
Linopirdine (**3**) is a pharmacologically potent and orally active cognitive enhancer in phase III clinical trials which acts by stimulation of neurotransmitter release in the central nervous system [1-3]. We have recently developed a large-scale manufacturing process by which linopirdine is synthesized in seven chemical steps from diphenylamine and oxalyl chloride [4,5]. In our original linopirdine process, we reduced 3-ene-2-oxindole **1** to oxindole **2** by catalytic transfer hydrogenation, using formic acid and palladium on carbon in 2-propanol. Catalytic hydrogenation of 3-ene-2-oxindoles (isatylidenes) is well known [6-8] and in our hands gave some overreduction of the pyridine ring. For scale-up, we switched to sodium borohydride in methanol as the reducing agent which allowed us to use existing equipment to convert **1** to **3** without isolation of **2** (Scheme 1). Although the overall conversion is high (~95%), a number of minor impurities are detected in the combined reduction and alkylation steps. Other than the self condensation of 4-picolyl chloride [9,10], the by-products are all formed during the reduction step.

Scheme 1



During the reduction of **1** in methanol, several of the detected by-products can be rationalized as Michael adducts, oxidation, or hydrolysis products of **1** and **2** (Scheme 2). Upon dissolution of the *E* isomer of **1** in methanol, three new peaks are observed by hplc. One product is simply the *Z* isomer of **1**, which is more soluble than the *E* isomer, and forms about 30% of the product distribution at equilibrium. Its formation is catalyzed by protic solvents and acids or bases. The *E* to *Z* isomerization of isatylidenes is well known and the configurations are assignable by ^{1}H nmr [7,11]. Additionally, we have obtained a single crystal X-ray structure for the *E* isomer of **1** [12]. The other two products formed in methanol, observable by hplc, have not been isolated, but are believed to be the diastereomeric reversible methanol addition adducts, **4a, 4b**. These are probably intermediates of the *E* to *Z* isomerization since the rate of isomerization is much slower in polar aprotic solvents. At equilibrium, the adducts repre-

Scheme 2



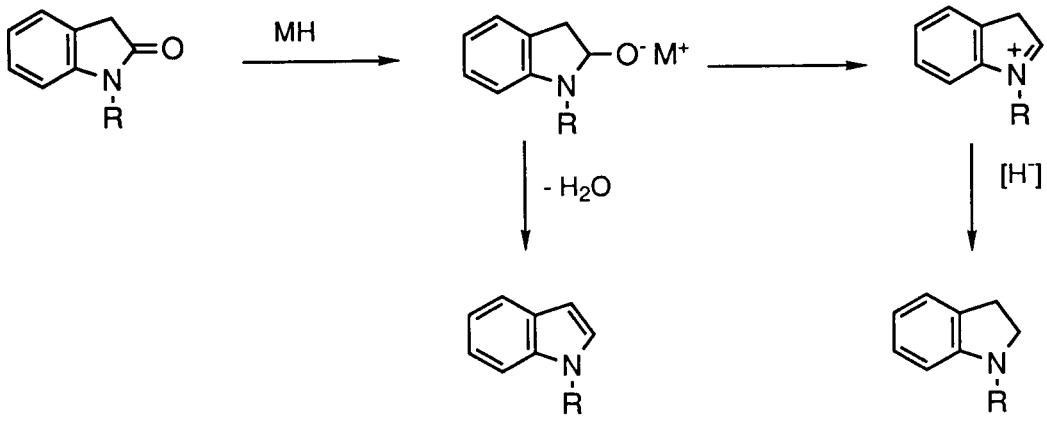
sent about 7% of the product distribution and they are consumed during the sodium borohydride reduction process. Michael additions to isatylidenes are well known reactions [6,13,14] and β-alkoxycarbinols are common by-products in the sodium borohydride reduction of α,β-unsaturated ketones in alcoholic solvents [15,16]. In the reduction of **1**, however, the reverse Michael reaction must be faster than 1,2-reduction of the oxindole as the conversion to **2** is high and no methoxy products have been detected after reduction.

Products **5a** and **5b** are formed by Michael addition of **2** onto **1**. These products (mixture of diastereomeric pairs) have been noted during the reduction step by hplc. They are in equilibrium with **1** and **2** and are consumed during the reduction. On occasion the dimers have precipitated thus requiring a longer reaction period to be consumed. One of the diastereomers of **5** has been isolated and characterized by liquid chromatography-ms and ^{1}H nmr, though the relative stereochemistry is unknown. The other diastereomer **5b** could not be isolated pure but its ms and uv were identical with **5a**. Although oxindoles are known to be Michael donors [8,17], to our knowledge, this is the first example of Michael adduct formation between an oxindole and an isatylidene. The acidity at the 3-position and high nucleophilicity of the anion of **2** are further demonstrated by the extremely facile air oxidation of **2** to **6** under mildly basic conditions [18]. This product is easily formed even in the presence of excess reducing agent so air must be carefully excluded during the borohydride reduction of **1**. Under the normal reduction conditions (*p*H ~12), the saponification products **7** and **8** have not been observed. Although **7** can be prepared in good yield by treatment of **2** with excess potassium hydroxide, the corresponding hydrolysis of **6** to **8** could not be driven to completion, and after acidification, largely reconverted to **6**. Treatment of **7** with air under basic conditions did not lead to formation of **8**.

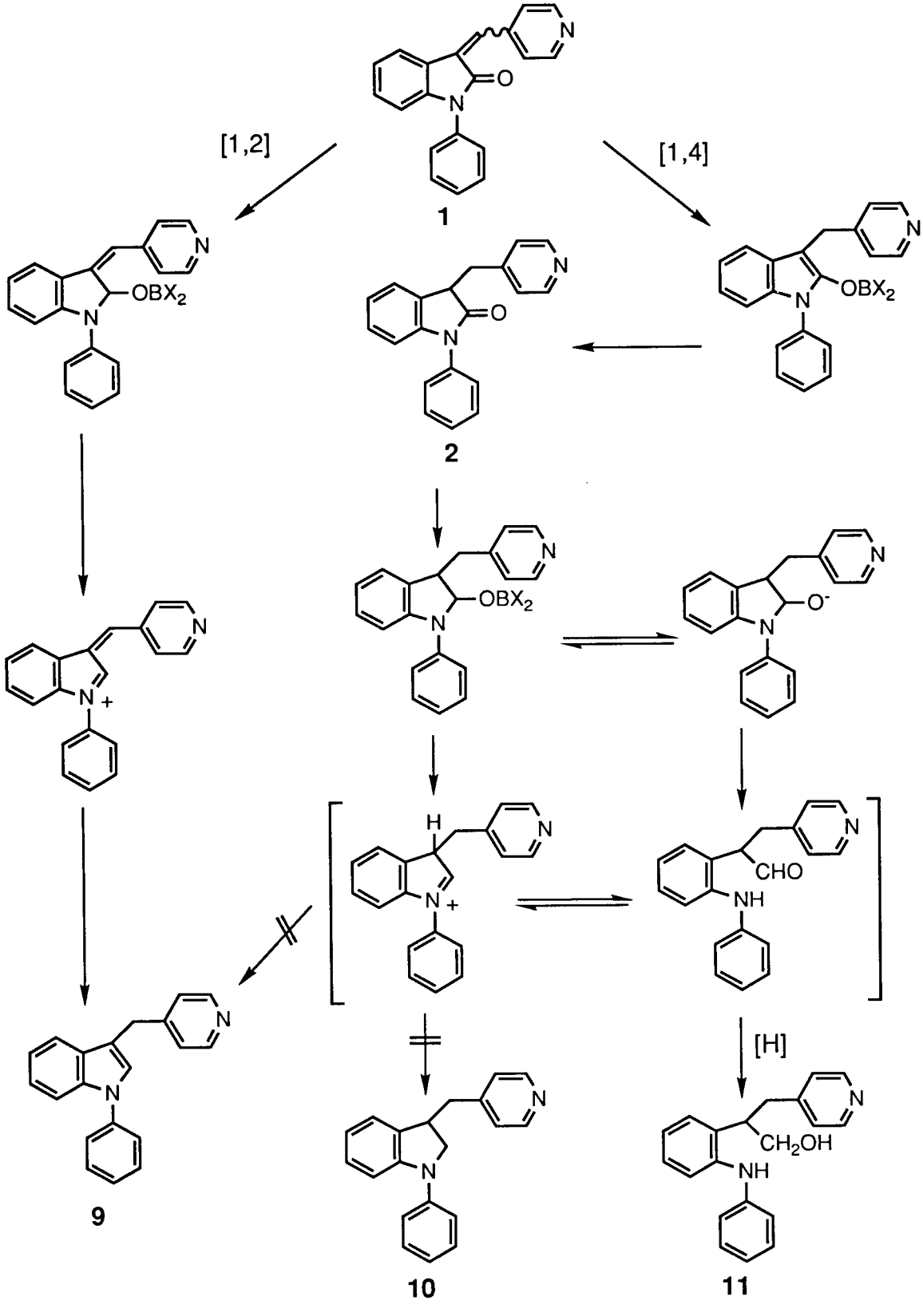
We investigated a variety of solvents for the sodium borohydride reduction of **1** to **2**, including 2-propanol, ethanol, methanol, water, tetrahydrofuran, and pyridine. Surprisingly, attempted reduction of **1** in 2-propanol (or ethanol) gave very little reaction, even when heated to reflux; however, the reductions in methanol or highly enriched methanol/2-propanol or methanol/water mixtures proceeded readily at room temperature. This indicates that methoxy borohydride species are the active reducing agents. Monitoring the evolution of hydrogen during the reduction of **1** with sodium borohydride in methanol showed approximately one equivalent evolved. Also, the minimum stoichiometry of sodium borohydride to give complete reduction of **1** (0.37 mole, 1.49 equivalents of hydride) further suggests the formation of a sodium methoxyborohydride species prior to reduction. This may not be the complete explanation regarding reactivity since there is a gradual increase in reactivity with increasing methanol concentration in methanol/2-propanol mixtures. For example, a 23% methanol/2-propanol mixture required heating to 86° to complete the reaction even though there were 32 moles of methanol per mole of sodium borohydride. There is literature precedent for the increased reactivity of sodium methoxyborohydride species over sodium borohydride both for the reduction of epoxides [19] and α,β-unsaturated nitro compounds [20]. Although the reduction of **1** to **2** can be accomplished with technical grade sodium trimethoxyborohydride in either methanol or tetrahydrofuran, the rate is slower than with sodium borohydride in methanol. Sodium borohydride in pyridine is reported to give only 1,4-reduction of α,β-enones [15,21]; however, when **1** was reacted in pyridine, the reduction did not go to completion and various unidentified by-products were formed.

Although sodium borohydride typically gives a preponderence of 1,4-addition to α,β-unsaturated enones, there are few literature examples for its use in the reduction of isatylidenes [22,23]. As with the catalytic hydrogenation method and with examples utilizing other reducing agents [24,25], no discussion of major synthetic by-products has been given. As expected, we find that the predominant re-

Scheme 3



Scheme 4



action pathway with **1** is 1,4-reduction as evidenced by the high conversion to oxindole **2**. Others have found that reduction of 2-oxindoles and 3-hydroxyoxindoles under a variety of conditions gives mixtures of indole and indoline products, which are believed to be derived from dehydration of the carbinolamine or competing elimination/reduction reactions as shown in Scheme 3 [25-28].

The major by-products formed during the reduction of **1** with sodium borohydride are indole **9** and the ring opened product, **11**, each representing about 2% of the product composition (Scheme 4). In contrast with what one would expect from the mechanism proposed in Scheme 3, indole **9** is not derived from overreduction of **2**, but is formed concurrently. When **2** is reacted with sodium borohydride or sodium acetoxyborohydride, with varying amounts of sodium hydroxide, in tetrahydrofuran or methanol, no discernable conversion to **9** is observed. With sodium acetoxyborohydride, an isolable boron complex formed that could be hydrolyzed back to **2**. With excess sodium borohydride in basic solutions, the hydroxymethyl product **11** was formed exclusively. One possible mechanism, based on initial 1,2-addition to **1**, followed by direct elimination of the β-ene, α-boronic ester to give the ene iminium salt followed by either conjugate reduction or direct reduction of the iminium salt, followed by olefin isomerization gives **9** (Scheme 4). Distinguishing between 1,4- or 1,2-hydride addition followed by rearrangement would be difficult since 3-methylenindolines easily isomerize to the corresponding indoles [29,30]. An attempt to induce 1,2-hydride addition to **1** by adding cerous chloride to the sodium borohydride/methanol reaction only led to considerable evolution of hydrogen and a mixture of **1** and **2**. Under these Lewis acid conditions, no **9**, **11** nor any of the Michael adducts **5a** and **5b** were observed. The best method we have found to synthesize **9** is reduction of **2** with borane-dimethyl sulfide complex in refluxing tetrahydrofuran and isolating the product as its hydrochloride salt.

Compound **11**, which can be synthesized by treating either **1** or **2** with excess sodium borohydride in base stabilized methanol, is believed to proceed through the iminium salt intermediate. Solvolysis followed by reduction of the resulting aldehyde gives **11**. Although solvolysis to the aldehyde would be expected to predominate over elimination or hydride attack under basic conditions (similar to cyanohydrin cleavage), the use of excess sodium hydroxide actually decreases the reaction rate, but not the overall conversion to **11**. The possibility that amide **2** is solvolyzed with methanol/water/base and the resulting aminocarboxylate **7** reduced to **11** is discounted as the rate of **11** formation, under the reaction conditions, is about 20 times that of solvolysis. Additionally carboxylate **7**, prepared separately by treating **2** with potassium hydroxide/methanol was inert to reaction with sodium borohydride.

Although 2-aminophenethyl alcohols can be readily prepared from 2-nitrotoluenes [31,32], the unexpected reduction of **2** to **11** allows the efficient preparation of highly substituted products, which heretofore has been unexplored.

EXPERIMENTAL

General Methods.

Melting points are uncorrected. The ^{1}H nmr spectra were determined with Varian XL-300 or Gemini 300 spectrometers operating at 299.95 MHz; chemical shifts are expressed in ppm (δ) downfield from TMS. High resolution mass spectra were obtained on a VG 70-VSE mass spectrometer. Elemental analyses were performed by Quantitative Technologies, Inc., Bound Brook, New Jersey. The hplc analyses were performed using reversed-phase conditions with Hewlett Packard HP1090M instuments, equipped with diode array detectors. The liquid chromatography-ms analyses were run on a Finnigen 4500 with thermospray interface. All reactions were run under nitrogen and all reagents were reagent grade unless otherwise noted.

1,3-Dihydro-1-phenyl-3-(4-pyridinylmethyl)-2*H*-indol-2-one (**2**).

2-Propanol (1085 ml), 50% palladium on carbon (30 g), and **1** (200 g, 671 mmoles) were stirred at reflux as 96% formic acid (44 ml, 1.17 moles) was added over two hours. The resulting mixture was filtered through diatomaceous earth, heated to 55°, and stirred as concentrated hydrochloric acid (88.3 ml, 1.06 moles) was slowly added. The resulting slurry was cooled in an ice bath and the product isolated by vacuum filtration. The crude product was washed with 2-propanol (600 ml), then reslurried at 10-15° with 600 ml fresh 2-propanol, refiltered and dried *in vacuo* at 60° for four hours to give 200 g (89%) of the hydrochloride salt of **2**. A 2 ℓ Erlenmeyer flask was charged with 100 g of the hydrochloride salt of **2** and methylene chloride (450 ml). The mixture was stirred while 500 ml of 1 *N* sodium hydroxide was added. After stirring 15 minutes, the phases were separated. The organic phase was washed twice with water, dried with magnesium sulfate and stripped *in vacuo* to yield 88 g (99% yield) of **2** as an off-white solid, mp 106-108°; ^{1}H nmr (deuteriochloroform): δ 3.27 (m, 1H), 3.45 (m, 1H), 3.96 (m, 1H), 6.65 (d, 1H, J = 7.5 Hz), 7.0-7.6 (complex, 10H), 8.45 (d, 2H, J = 7 Hz).

Anal. Calcd. for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 79.75; H, 5.40; N, 9.29.

General Reduction and Alkylation Procedure to Give 3,3-Bis(4-pyridinylmethyl)-1-phenyl-2*H*-indolin-2-one, Linopirdine (**3**).

Methanol (259 g, 327 ml) and **1** [3] (107.7 g, 361 mmoles) were charged into a 1 ℓ four neck round-bottomed flask equipped with mechanical stirred, thermocouple probe, condenser with nitrogen inlet and 50 ml addition funnel. Separately, a solution of 30% sodium hydroxide (0.36 g, 0.28 ml) and sodium borohydride (6.3 g, 167 mmoles) in water (31.8 ml) was prepared. The sodium borohydride solution was added to the methanolic slurry of **1** *via* the addition funnel over 60 minutes at 27-31°. After stirring at ambient temperature for 30 minutes, the slurry was heated to 35° and held 30 minutes then heated to 55° for 30 minutes giving a brown solution. The solution was cooled to 10°, then diluted with

water (90 ml) and 30% sodium hydroxide (119 g, 90 ml). A solution of technical grade 4-picolyl chloride hydrochloride (66 g, 402 mmoles) in water (99 ml) was added over 60 minutes at 20-25°. After stirring 1 hour at ambient temperature, water (200 ml) was added over 1 hour. The resulting slurry was stirred overnight at ambient temperature then vacuum filtered. The product was washed twice with 100 ml portions of water then dried overnight *in vacuo* at 50° with a slight nitrogen purge, yield 131.0 g, 93%; hplc, 92.7 area %. Purification and characterization of this material is described in reference 5.

(+/−)-3-((1-(2,3-Dihydro-2-oxo-1-phenyl-1*H*-indol-3-yl)-1-(4-pyridinyl)methyl))-1,3-dihydro-1-phenyl-3-(4-pyridinylmethyl)-2*H*-indol-2-one (**5a**).

Methanol (10 ml), **1** (2.98 g, 10 mmoles), **2** (3.00 g, 10 mmoles), and 50% sodium hydroxide (0.2 g, 2.5 mmoles) were combined and refluxed under nitrogen for two hours, then cooled to room temperature and the resulting slurry stirred for 10 days. The product was isolated by vacuum filtration, washed with methanol and dried *in vacuo* at 40° for four hours to give 4.35 g (73%) of **5a** as an off-white solid, mp 178-181°; ^{1}H nmr (deuteriochloroform): δ 3.26 (q, 2H, J = 15 Hz), 3.84 (d, 1H, J = 4 Hz), 4.37 (d, 1H, J = 4 Hz), 6.54 (m, 2H), 6.72 (d, 2H, J = 6 Hz), 6.83 (d, 2H, J = 7.5 Hz), 6.9-7.5 (complex, 15H), 7.83 (d, 1H, J = 7 Hz), 8.27 (d, 2H, J = 6.5 Hz), 8.43 (d, 2H, J = 6.5 Hz).

Anal. Calcd. for $C_{40}H_{30}N_4O_2$: C, 80.25; H, 5.05; N, 9.36. Found: C, 79.97; H, 5.02; N, 9.26.

1,3-Dihydro-3-hydroxy-1-phenyl-3-(4-pyridinylmethyl)-2*H*-indol-2-one (**6**).

Methanol (120 ml), 50% sodium hydroxide (0.30 g), and oxindole **2** (12.0 g) were stirred in a 125 ml Erlenmeyer flask for three hours while bubbling air through the mixture. The resulting slurry was filtered and the solids washed with methanol and water. The product was dried to afford 11.1 g (88%) crude **6**. An analytical sample was prepared by recrystallization from methanol, mp 207.5-208.5°; ^{1}H nmr (deuteriochloroform): δ 3.37 (q, 2H, J = 12 Hz), 4.30 (s, 1H), 6.55 (d, 1H, J = 7.5 Hz), 6.8-7.5 (complex, 10H), 8.28 (dd, 2H, J = 2, 7 Hz).

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.54; H, 4.96; N, 8.74.

[2-(Phenylamino)phenyl]-3-(4-pyridine)propionic Acid (**7**).

Methanol (50 ml), 87% potassium hydroxide (10 g, 155 mmoles) and **2** (10.0 g, 33.3 mmoles) were combined in a 100 ml round-bottomed flask equipped with magnetic stirrer and refluxed under nitrogen for nine hours. The solution was neutralized with 37% hydrochloric acid (13 ml, 156 mmoles) and diluted with 40 ml water. The product was filtered, washed with water, reslurried with methanol and air dried to yield 9.4 g (89%) crude **7**. The crude product was partitioned between 40 ml of methylene chloride and 60 ml of 0.67 *N* sodium hydroxide. The aqueous phase was washed with fresh methylene chloride, clarified and acidified with acetic acid, to give, after filtration, water washing and drying *in vacuo* at 40°, 8.4 g of **7** (80%, 96.7% pure by hplc). An analytical sample was prepared by recrystallization from dimethylacetamide/water, mp 177-178.5°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.96 (m, 1H), 3.26 (m, 1H), 3.4 (brs, 1H), 4.40 (t, 1H, J = 7.5 Hz), 6.78 (m, 3H), 7.0-7.4 (complex, 8H), 7.6 (brs, 1H), 8.40 (d, 2H, J = 7 Hz).

Anal. Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.07; H, 5.65; N, 8.77.

1-Phenyl-3-(4-pyridinylmethyl)-1*H*-indole, Hydrochloride (**9**).

A 2-ℓ round-bottom flask was fitted with a condenser, overhead stirrer, temperature controller, and nitrogen inlet, then charged with oxindole **6** (98 g, 0.31 mole) and tetrahydrofuran (1100 ml). Subsequently, 10 *N* borane-dimethyl sulfide complex (100 ml) was added while cooling to maintain the temperature below 25°. The solution was stirred at room temperature for 6.5 hours, and then heated to reflux for 21 hours. After cooling to ambient temperature, water (44 ml) was added and the mixture stirred at room temperature overnight. The reaction was reheated to reflux for 72 hours, cooled to room temperature and filtered to remove precipitated boric acid. The solids were washed with tetrahydrofuran, and the combined filtrate and washes stripped to a yellow oil. The oil was dissolved in methylene chloride, washed with 1 *N* sodium hydroxide, washed with water, dried with magnesium sulfate, and evaporated to a yellow oil (65.4 g, 73%). The oil was dissolved in 1-chlorobutane (500 ml), charged into a 1-ℓ round-bottom flask fitted with condenser, overhead stirred, temperature controller, and nitrogen inlet, cooled to 5°, and sparged with hydrogen chloride over 15 minutes. After stirring overnight at room temperature, the product was filtered, washed with 1-chlorobutane, and dried *in vacuo* to give 59 g (98%) of light yellow solid, mp 207-210° dec; ^{1}H nmr (deuteriodichloromethane): δ 8.61 (d, 2H, J = 2 Hz), 7.82 (d, 2H, J = 2 Hz), 7.59-7.14 (complex, 12H), 4.45 (s, 2H).

Anal. Calcd. for $C_{20}H_{16}N_2HCl$. C, 74.64; H, 5.64; N, 8.70; Cl, 11.02. Found: C, 74.61; H, 5.24; N, 8.60; Cl, 11.14.

[2-(Phenylamino)phenyl]-3-(4-pyridine)propanol (**11**).

Methanol (100 ml) and **1** (10.0 g, 34 mmoles) were charged into a 250 ml 3-neck round-bottomed flask equipped with thermocouple probe, 100 ml addition funnel and a condenser with nitrogen inlet. Separately, a solution of sodium borohydride (8.5 g, 225 mmoles), 30% sodium hydroxide (~1 ml) and deionized water (50 ml) was prepared. The sodium borohydride solution was added to the methanolic slurry of **1** over 5 minutes, giving a yellow brown solution. The solution was heated to 40° and held for one hour then stirred overnight at room temperature. After heating one hour at 60°, the mixture was diluted with toluene (75 ml) and water (50 ml) and then heated to reflux as 100 ml of solvent was distilled. Toluene (50 ml) was added and the phases separated. The organic phase was washed twice with 50 ml portions of water and then concentrated to a thick oil which partially crystallized upon standing overnight. The residue was cooled in an ice bath and triturated twice with 10 ml portions of cold toluene to afford 8.32 g (82%) of product, mp 95-95.4°; hplc, 99.8 area %; ^{1}H nmr (deuteriochloroform): δ 8.30 (d, 2H, J = 5.7 Hz), 7.3-6.7 (complex, 12H), 6.01 (brs, 1H), 3.81 (d of multiplets, 2H), 3.56 (m, 1H), 2.97 (d of multiplets, 2H); hrms Calcd. 305.1654. Found: 305.1647.

Anal. Calcd. for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.80; H, 6.57; N, 9.09.

REFERENCES AND NOTES

[1] V. J. Nickolson, S. W. Tam, M. J. Meyers and L. Cook, *Drug Dev. Res.*, **19**, 285 (1990).

[2] S. W. Tam, D. Rominger and V. J. Nickolson, *Mol. Pharmacol.*, **40**, 16 (1991).

[3] K. F. DeNoble, V. J. DeNoble and K. R. Spencer, *Brain Res. Bull.*, **26**, 817 (1991).

[4] W. M. Bryant and G. F. Huhn, U. S. Patent 4806651, (1989); *Chem. Abstr.*, **111**, 57536u (1990).

[5] W. M. Bryant, G. F. Huhn, J. H. Jensen, M. E. Pierce and C. Stammbach, *Synth. Commun.*, **23**, 1617 (1993).

[6] E. Wenkert, J. H. Udelhofen and N. K. Bhattacharyya, *J. Am. Chem. Soc.*, **81**, 3763 (1959).

[7] R. L. Autrey and F. C. Tahk, *Tetrahedron*, **23**, 901 (1967).

[8] P. L. Julian and H. C. Printy, *J. Am. Chem. Soc.*, **75**, 5301 (1953).

[9] S. C. Shim and S. S. Kim, *Bull. Korean Chem. Soc.*, **3**, 110 (1982).

[10] The major product of self condensation under our conditions is the dimer as determined by liquid chromatography-mass spectroscopy. Reference 6 indicates that under aprotic conditions, the major products are the cyclic hexamer and linear polymers.

[11] D. R. Long, C. G. Richards and M. S. F. Ross, *J. Heterocyclic Chem.*, **15**, 633 (1978).

[12] Crystal Data and Structural Analysis of **1**. $C_{20}H_{14}N_2O$. Yellow needle, 0.14 x 0.15 x 0.51 mm, triclinic, P_1 (No. 2), a = 12.238 (4), b = 13.793 (4), c = 9.710 (3) Angstroms, β = 98.43 (2), γ = 103.21 (2)° from 19 reflections, T = −100°, V = 1463.9 cubic angstroms, Z = 4, FW = 298.35, Dc = 1.353g/cc, μ(Mo) = 0.79 cm^{-1}. Data collected on a Syntex R3 diffractometer, graphite monochronometer, MoKα radiation. Structure solved by MULTAN. R = 0.044, Rw = 0.037. Error of fit = 1.10. Unique reflections = 2183. Refinement by full-matrix least squares.

[13] H. Pleininger and C. E. Castro, *Chem. Ber.*, **87**, 1760 (1954).

[14] G. Tacconi, A. Gamba, F. Marinone and G. Desimoni, *Tetrahedron*, **27**, 561 (1971).

[15] W. R. Jackson and A. Zurqiyah, *J. Chem. Soc.*, 5280 (1965).

[16] M. R. Johnson and B. Rickborn, *J. Org. Chem.*, **35**, 1041 (1970).

[17] G. Palazzo and V. Rosnati, *Gazz. Chim. Ital.*, 584 (1952).

[18] T. Nishio, *J. Chem. Soc., Perkin Trans. 1*, 1717 (1991).

[19] K. Soai, A. Ookawa, H. Oyamada and M. Takase, *Heterocycles*, **19**, 1371 (1982).

[20] R. S. Varma and G. W. Kabalka, *Synth. Commun.*, **15**, 151 (1985).

[21] S. B. Kadin, *J. Org. Chem.*, **31**, 620 (1966).

[22] M. Mori and Y. Ban, *Tetrahedron Letters*, 1133 (1979).

[23] J. W. Elliott and P. Rivers, *J. Org. Chem.*, **29**, 2438 (1964).

[24] K. Okada, H. Tanino, K. Hashizume, M. Mizuno, H. Kakoi and S. Inoue, *Tetrahedron Letters*, **25**, 4403 (1984).

[25] E. Wenkert, B. S. Bernstein and J. H. Udelhofen, *J. Am. Chem. Soc.*, **80**, 4899 (1959).

[26] T. Nishio, N. Okuda and C. Kashima, *Helv. Chim. Acta*, **73**, 1719 (1990).

[27] H. Sirowej, S. A. Khan and H. Pleininger, *Synthesis*, 84 (1972).

[28] A. M. Akkerman and H. Veldstra, *Recl. Trav. Chim. Pays-Bas*, **74**, 629 (1954).

[29] D. L. Bolger, T. Ishizaki, P. A. Kitos and O. Suntornwat, *J. Org. Chem.*, **55**, 5823 (1990).

[30] J. H. Tidwell, D. R. Senn and S. L. Buchwals, *J. Am. Chem. Soc.*, **113**, 4685 (1991).

[31] G. M. Bennett and M. M. Hafez, *J. Chem. Soc.*, 287 (1941).

[32] Y. Tsuji, S. Kotachi, K.-T. Huh and Y. Watanabe, *J. Org. Chem.*, **55**, 580 (1990).