SYNTHESIS OF 2-(4-PIPERIDYLMETHYL)INDOLES. INTERMEDIATES FOR THE SYNTHESIS OF *STRYCHNOS* ALKALOIDS

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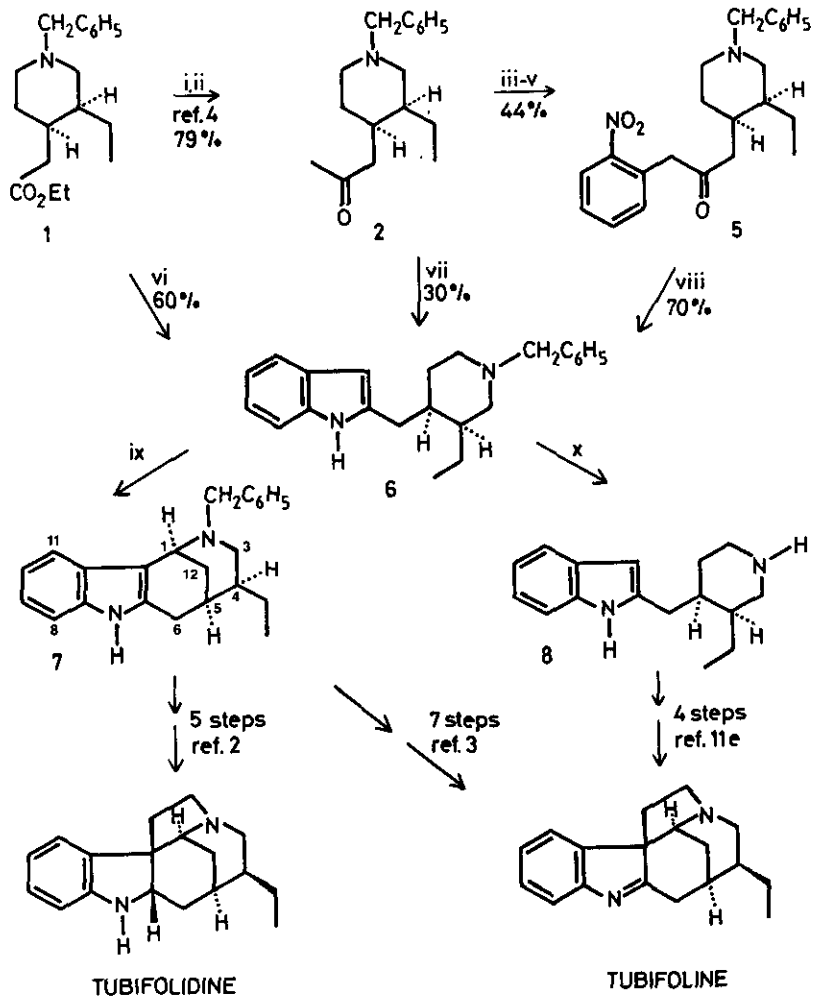
Abstract—The synthesis of 2-[(*cis*-1-benzyl-3-ethyl-4-piperidyl)-methyl]indole (**6**) by three alternative procedures is reported, the condensation of the organodilithium derivative of *N*-trimethylsilyl-*o*-toluidine with ethyl *cis*-1-benzyl-3-ethyl-4-piperidineacetate (**1**) being the most efficient method. The indole derivative **6** has been converted into azocinoindole **7** by oxidative cyclization with mercuric acetate and into piperidylmethylindole **8** by debenzylation. Compounds **7** and **8** are known intermediates in previous syntheses of the *Strychnos* indole alkaloids tubifolidine and tubifoline.

In a previous paper we reported that the tetracyclic hexahydro-1,5-methanoazocino-[4,3-*b*]indole ring system, a substructure of *Strychnos* alkaloids, is accessible by mercuric acetate oxidation of 2-(4-piperidylmethyl)indoles.[1] With the final aim of preparing the tetracyclic base **7** by this procedure, which has just been synthesized by another route and elaborated into the alkaloids tubifolidine[2] and tubifoline[3], we have explored different approaches to the key intermediate 2-[(*cis*-1-benzyl-3-ethyl-4-piperidyl)methyl]indole (**6**).

Initially, we effected the Fischer indolization of *cis*-acetonylpiperidine **2**.[4] As could be expected, the reaction lacked regioselectivity[5] and a nearly equimolecular mixture of the desired indole derivative **6** (30% yield) and the 2,3-disubstituted indole **9** was formed.

In order to achieve the regiocontrol of the process we focused our attention on the reductive cyclization of α-(*o*-nitrophenyl)ketone **5**. This ketone was prepared by nuclear substitution onto *o*-fluoronitrobenzene using the enolate of ß-keto ester **3** followed by demethoxycarbonylation of the resulting arylated ß-keto ester **4**.[6] Hydrogenation of nitrobenzyl ketone **5** over platinum furnished piperidylmethylindole **6** in 70% yield.[7,8] Although this sequence allowed the unequivocal synthesis of the indole derivative **6**, the overall yield from acetonylpiperidine **2** was only



Reagents: (i) DMSO, NaH; (ii) Zn, AcOH; (iii) Me_2CO_3, NaH, THF; (iv) o-$FC_6H_4NO_2$, NaH, HMPA; (v) 3N HCl; (vi) o-$MeC_6H_4NHSiMe_3$, 2 equiv. BuLi; (vii) $C_6H_5NHNH_2$, Na_2CO_3; then PPA; (viii) H_2, PtO_2; (ix) $Hg(OAc)_2$, EDTA.2Na.$2H_2O$; then $NaBH_4$; (x) H_2, $Pd(OH)_2$.

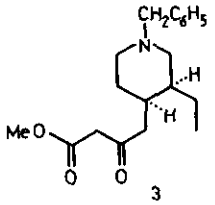
similar to that obtained by Fischer indolization.

Finally, we applied the method recently developed by Smith[9] for the elaboration of the indole nucleus, based on the condensation of the organodilithium derivative of N-trimethylsilyl-o-toluidine with esters. In our case, the direct conversion of ester 1 into piperidylmethylindole 6 resulted in 60% yield, which clearly improves those obtained by the above two procedures. Due to the mild conditions required for this reaction, the process seems to be more general than the tandem Boudroux-Madelung reactions that had been developed for the synthesis of an epimeric mix-

ture of **6** and its trans isomer[10,11] starting from a cis-trans mixture of 1-benzyl-3-ethyl-4-piperidineacetates. In the ^{13}C-nmr spectrum of piperidine **6** as well as in the spectra of all N-benzyl-cis-3,4-disubstituted piperidines described in this paper, the absorptions due to C-4, C-6, and the methylene carbons attached to C-3 and C-4 appear as broad signals due to the conformational inversion of the piperidine ring.[12]

Oxidative cyclization of **6** was effected with mercuric acetate at pH 3-4 in water as the solvent,[13] in the presence of EDTA disodium salt to avoid the mercuriation of the indole nucleus. Careful purification of the reaction mixture allowed the isolation of azocinoindole **7**, whose structure was evident from its spectroscopic data. The most significant signal in the ^{1}H-nmr spectrum of **7** is an apparent triplet at δ4.29 due to the bridgehead C-1 methine proton, thus clearly indicating that compound **7**, having the ethyl chain at the C-4 position, had been obtained. The equatorial disposition of the ethyl substituent was inferred taking into account the shielding (-4.8 ppm) of C-6 in the ^{13}C-nmr spectrum by a γ-effect as compared with the base value in the corresponding deethyl analogue.[1] The azocinoindole **7** exhibited ir, nmr, and tlc Rf values identical to those of an authentic sample prepared by an independent route that culminated in the synthesis of the indole alkaloids tubifolidine[2] and tubifoline.[3]

On the other hand, removal of the N-benzyl group present in piperidine **6** by hydrogenolysis over Pearlman's catalyst[14] yielded the known secondary amine **8**, an intermediate in the Snieckus synthesis of tubifoline.[11e]



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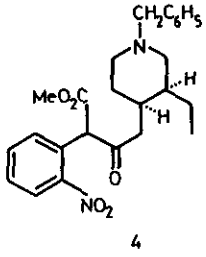

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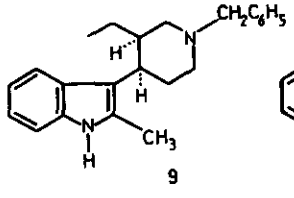

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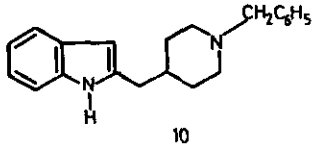

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EXPERIMENTAL

The nmr spectra were recorded in $CDCl_3$ on a Varian XL-200 spectrometer with TMS as internal standard. Chemical shifts are reported in ppm (δ) downfield from TMS. Ir spectra were taken with a Perkin-Elmer 1430 spectrophotometer and only noteworthy absorptions (reciprocal centimeters) are listed. Tlc was carried out on SiO_2 (silica gel 60, Merck 0.063-0.200 mm), and the spots were

located with uv light or iodoplatinate reagent. Flash chromatography was carried out on SiO_2 (silica gel 60, 0.040–0.063 mm, Macherey-Nagel). Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous sodium sulfate powder. Microanalyses were performed on a Carlo Erba 1106 analyzer by Departamento de Química Orgánica Biológica, Barcelona.

Methyl cis-1-Benzyl-3-ethyl-4-piperidineacetoacetate (3)

To a warmed suspension of sodium hydride (3.66 g, 55%, 83 mmol), previously washed with hexane, in THF (280 ml) were slowly added in a sequential manner, dimethyl carbonate (7 ml, 83 mmol), a few drops of methanol, and a solution of ketone **2**[4] (7.25 g, 27.9 mmol) in THF. The mixture was refluxed for 8 h, cooled, and brought to pH 6–7 by careful addition (0°C) of concentrated acetic acid. Cold water was added and the mixture was basified with concentrated ammonium hydroxide. The organic layer was separated and the aqueous phase was extracted with methylene chloride. The combined organic extracts were dried and evaporated. Flash chromatography (methylene chloride) gave pure ß-keto ester **3** (7.8 g, 88%) as an oil; ir ($CHCl_3$) 1740 (strong, CO ester), 1710 (strong, CO ketone), 1650 (weak, enol ester), 1625 (weak, C=C enol); ^{1}H-nmr 0.81 (t, J = 7 Hz, 3H, CH_3), 2.51 (d, J = 6.5 Hz, 2H, CH_2CO), 3.40 and 3.55 (2d, J = 13 Hz, 1H each, CH_2Ar), 3.47 (s, 2H, $COCH_2CO$), 3.76 (s, 3H, OCH_3), 7.27–7.34 (m, 5H, ArH); ^{13}C-nmr 12.0 (CH_3), 20.1 (br, CH_2), 28.5 (5-C), 33.2 (br, 4-C), 40.0 (3-C), 44.1 (br, 4-CH_2), 49.5 ($CO\underline{C}H_2CO$), 52.3 (OCH_3), 52.3 (br, 6-C), 55.4 (2-C), 63.3 (CH_2Ar), 126.8 (p-Ar), 128.1 (m-Ar), 128.9 (o-Ar), 138.9 (ipso-C). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.88; H, 8.57; N, 4.41. Found: C, 71.74; H, 8.84; N, 4.34.

Methyl 4-(cis-1-Benzyl-3-ethyl-4-piperidyl)-2-(o-nitrophenyl)-3-oxobutyrate (4)

To a suspension of sodium hydride (511 mg, 55%, 11.7 mmol), previously washed with hexane, in HMPA (20 ml) was added under nitrogen a solution of ß-keto ester **3** (1.86 g, 5.8 mmol) in HMPA (2 ml). The mixture was warmed at 60–70°C. When the evolution of hydrogen ceased, o-fluoronitrobenzene (0.75 ml, 7 mmol) was added. The reaction mixture was stirred at 60–70°C for 2 h, cooled, diluted with brine, and extracted several times with ether. The ethereal solution was exhaustively washed with brine, dried, and evaporated. Flash chromatography (98:2 methylene chloride–methanol) gave pure arylated ß-keto ester **4** (1.62 g, 63%); ir ($CHCl_3$) 1715–1735 (weak, CO), 1650 (strong, CO enol ester), 1610 (strong, C=C enol), 1520 and 1350 (NO_2); ^{1}H-nmr[6] 0.58 and 0.71 (2t of similar intensity, J = 7 Hz, 3H, CH_3), 3.30 and 3.46 (2d, J = 13 Hz, 2H, NCH_2Ar), 3.63 and 3.77 (2s, 3H, OCH_3), 7.22–7.30 (m, 6H, ArH), 7.49–7.70 (m, 2H, 4′- and 5′-H), 8.05 (m, 1H, 3′-H); ^{13}C-nmr[6] 11.8 (CH_3), 20.1 (br, CH_2), 28.0 (5-C), 33.5 (br, 4-C), 35.5 (br, 4-CH_2), 40.0 (3-C), 52.1 (OCH_3), 52.9 (br, 6-C), 55.3 (2-C), 60.1 (weak, $CO\underline{C}HCO$), 63.2 (CH_2Ar), 101.5 ($\underline{C}$=C-OH), 115.9–134.1 (18 peaks), 138.9 (ipso-C), 149.6 (2′-C), 171.7 (C=$\underline{C}$-OH), 175.7 (COOMe). Anal. Calcd for $C_{25}H_{30}N_2O_5$: C, 68.47;

H, 6.89; N, 6.38. Found: C, 68.48; H, 7.05; N, 6.36.

1-(cis-1-Benzyl-3-ethyl-4-piperidyl)-3-(o-nitrophenyl)-2-propanone (5)

A solution of ß-keto ester **4** (1.5 g, 3.4 mmol) in 3 N hydrochloric acid (30 ml) was refluxed for 3 h. After cooling, the reaction mixture was basified with aqueous 2 N sodium hydroxide solution and extracted with methylene chloride. The combined organic extracts were dried and the solvent was evaporated. Purification of the residue by flash chromatography (99:1 methylene chloride-methanol)yielded pure ketone **5** (1.03 g, 80%); ir (NaCl) 1720 (CO), 1525 and 1350 (NO_2); ^{1}H-nmr 0.80 (t, J = 7 Hz, 3H, CH_3), 2.56 (d, J = 6.5 Hz, 2H, CH_2CO), 3.37 and 3.53 (2d, J = 13 Hz, 1H each, NCH_2Ar), 4.09 (s, 2H, $ArCH_2CO$), 7.22-7.41 (m, 6H, ArH), 7.45 (td, J = 8 and 1.5 Hz, 1H, 4'-H), 7.58 (td, J = 8 and 1.5 Hz, 1H, 5'-H), 8.10 (dd, J = 8 and 1.5 Hz, 1H, 3'-H); ^{13}C-nmr 12.0 (CH_3), 20.2 (br, CH_2), 28.6 (5-C), 33.2 (br, 4-C), 40.1 (3-C), 43.6 (br, 4-CH_2). 48.4 ($CO\underline{C}H_2CO$), 52.3 (br, 6-C), 55.4 (2-C), 63.3 (NCH_2Ar), 125.2 (3'-C), 126.8 (p-C), 128.1 (o-C), 128.3 (4'-C), 129.0 (m-C), 130.3 (1'-C), 133.5 (5'- and 6'-C), 138.8 (ipso-C), 148.7 (2'-C). Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.41; N, 7.37. Found: C, 72.29; H, 7.50; N, 7.11.

2-[(cis-1-Benzyl-3-ethyl-4-piperidyl)methyl]indole (6)

A. From ketone 2

Phenylhydrazine hydrochloride (1.42 g, 9.8 mmol) and anhydrous sodium carbonate (528 mg) were added to a stirred solution of ketone **2** (2.31 g, 8.9 mmol) in absolute ethanol (55 ml). The mixture was refluxed for 3 h. After cooling, the solvent was evaporated and the resulting residue was diluted with aqueous sodium carbonate solution and extracted with methylene chloride. Drying and evaporation of the organic extracts afforded the corresponding crude phenylhydrazone (3.1 g). A mixture of this hydrazone and polyphosphoric acid (31 g) was heated at 135°C with mechanical stirring for 1.5 h. Then, the mixture was poured into crushed ice, basified with aqueous sodium hydroxide solution, and extracted with ether. Evaporation of the extracts gave a syrup which was chromatographed on silica gel. On elution with hexane-chloroform (1:1), a mixture of the indole derivative **6** and its regioisomer **9**[15] was obtained. Further column chromatography of this mixture (elution with 9:1 hexane-ethyl acetate) furnished the indole **6** (888 mg, 30%); ^{1}H-nmr 0.81 (t, J = 7 Hz, 3H, CH_3), 2.65 (m, 2H, CH_2In), 3.37 and 3.54 (2d, J = 13 Hz, 1H each, NCH_2Ar), 6.21 (dd, J = 2.1 and 0.8 Hz, 1H, 3-H), 7.05-7.33 (m, 9H, ArH), 7.50 (br, 1H, NH); ^{13}C-nmr 12.1 (CH_3), 19.5 (br, CH_2), 28.0 (5'-C), 29.7 (br, CH_2In), 38.7 (br, 4'-C), 40.6 (3'-C), 52.8 (br, 6'-C), 55.2 (2'-C), 63.3 (NCH_2Ar), 100.4 (3-C), 110.3 (7-C), 119.5 and 119.7 (4- and 5-C), 121.0 (6-C), 126.8 (p-C), 128.1 (m-C), 128.1 (3a-C), 128.9 (o-C), 135.8 (2-C), 138.5 (7a-C), 138.9 (ipso-C). Anal. Calcd for $C_{23}H_{28}N_2.1/2H_2O$: C, 80.87; H, 8.50; N, 8.20. Found: C, 80.47; H, 8.54; N, 7.95.

B. From o-nitrobenzyl ketone 5

A solution of ketone **5** (150 mg, 0.39 mmol) in absolute ethanol (10 ml) was hydrogenated in the presence of platinum dioxide (70 mg) until the hydrogen absorption ceased (aproximately 10 min). The resulting mixture was filtered through Celite, evaporated, and purified by flash chromatography (97:3 methylene chloride-methanol) to give the indole **6** (91 mg, 70%).

C. From ester 1

The dilithium derivative of N-trimethylsilyl-o-toluidine was prepared, according to the procedure reported by Smith,[9] from N-trimethylsilyl-o-toluidine (0.95 g, 5.19 mmol), hexane (30 ml), and 1.6 M n-BuLi in hexanes (6.5 ml, 11.4 mmol). This dianion was then added via cannula to a precooled (-78°C) solution of ester **1**[4] (1 g, 3.46 mmol) in THF (15 ml). The mixture was allowed to warm to room temperature, quenched with brine, and extracted several times with ether. The organic extract was evaporated and the residue chromatographed (SiO_2). On elution with hexane-ethyl acetate (85:15), the indole **6** (689 mg, 60%) was obtained.

(1RS, 4RS, 5SR)-2-Benzyl-4-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (7)

A solution of **6** (3.32 g, 10 mmol) in methylene chloride (5 ml) was added to a solution of mercuric acetate (15.9 g, 49 mmol) and EDTA.Na_2.$2H_2O$ (19 g, 5.1 mmol) in water (300 ml). Methylene chloride was evaporated at 40°C under a stream of nitrogen and the resulting solution was refluxed for 1.5 h. After addition of methanol (80 ml) and sodium borohydride (335 mg), the whole was stirred at room temperature for 20 min and filtered. The filtrate was concentrated under reduced pressure, basified with aqueous ammonium hydroxide, and extracted with methylene chloride. Evaporation of the dried organic extracts gave an oil which was chromatographed twice through silica gel (elution with 9:1 chloroform-methanol) to give the azocinoindole **7** (220 mg, 7%); ^{1}H-nmr 0.86 (t, J = 7 Hz, 3H, CH_3), 2.72 (br s, 2H, 6-CH_2), 3.20 and 3.93 (2d, J = 14 Hz, 1H each, NCH_2Ar), 4.29 (apparent t, J = 3 Hz, 1H, 1-H), 7.09-7.40 (m, 9H, ArH), 8.10 (br, 1H, NH); ^{13}C-nmr 11.5 (CH_3), 22.6 (CH_2), 24.5 (6-C), 28.7 (5-C), 34.3 (12-C), 41.5 (4-C), 50.3 (3-C), 50.7 (1-C), 60.5 (NCH_2Ar), 106.8 (11b-C), 110.4 (8-C), 118.4 (11-C), 119.4 (10-C), 120.7 (9-C), 126.7(p-C), 128.1 (m-C), 128.5 (11a-C), 128.8 (o-C), 135.7 (6a-C), 136.7 (7a-C), 139.4 (ipso-C). The hydrochloride melted at 254-256°C (ethanol). Anal. Calcd for $C_{23}H_{27}ClN_2.1/3C_2H_6O$: C, 74.36; H, 7.64; N, 7.32; Cl, 9.27. Found: C, 73.95; H, 7.33; N, 7.42; Cl, 9.62.

2-[(cis-3-Ethyl-4-piperidyl)methyl]indole (8)

A suspension of benzyl derivative **6** (410 mg, 1.23 mmol) and 20% $Pd(OH)_2$ (Pearlman's catalyst) (40 mg) in ethanol (10 ml) was hydrogenated until total disappearance of the starting compound was

observed by tlc (95:5 methylene chloride-methanol). The catalyst was removed by filtration and the solvent evaporated. Purification by chromatography (SiO_2, 95:5 methylene chloride-methanol) yielded the known secondary amine **8**[11e] (178 mg, 60%); ^{1}H-nmr 0.94 (t, J = 7 Hz, 3H, CH_3), 1.2-1.7 (m, 5H), 2.1 (m, 1H, 4'-H), 2.5-2.8 (m, 4H, CH_2In, 2'- and 6'-Hax), 2.96 (dd, J = 12.5 and 6 Hz, 1H, 2'-Heq), 3.06 (dt, J = 12.5 and 5 Hz, 1H, 6'-Heq), 4.0 (br, 1H, NH), 6.24 (s, 1H, 3-H), 7.0-7.2 (m, 2H, 5- and 6-H), 7.31 (dd, J = 7 and 1.5 Hz, 1H, 7-H), 7.54 (dd, J = 7 and 1.5 Hz, 1H, 4-H), 8.3 (br, 1H, NH indole); ^{13}C-nmr 10.9 (CH_3), 18.3 (CH_2), 26.7 (5'-C), 28.0 (CH_2In), 37.0 (4'-C), 38.5 (3'-C), 43.1 (6'-C), 46.2 (2'-C), 99.4 (3-C), 109.4 (7-C), 118.5 and 118.6 (4- and 5-C), 119.9 (6-C), 127.8 (3a-C), 134.9 (2-C), 136.9 (7a-C).

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15. Compound **9**: nmr (60 MHz) 0.55 (t, J = 7 Hz, 3H, CH_3), 1.0-2.0 (m, 6H), 2.1 (s, 3H, In-CH_3), 2.4-3.2 (m, 4H, NCH_2), 3.27 and 3.54 (2d, J = 13 Hz, 1H each, NCH_2Ar), 6.6-7.6 (m, 10H, ArH).

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