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# SYNTHETIC ENTRY TO 8-(*o*-NITROPHENYL)-2-AZABICYCLO[3.3.1]NONAN-7-ONES. INTERMEDIATES FOR THE SYNTHESIS OF *STRYCHNOS*-TYPE SYSTEMS.[1]

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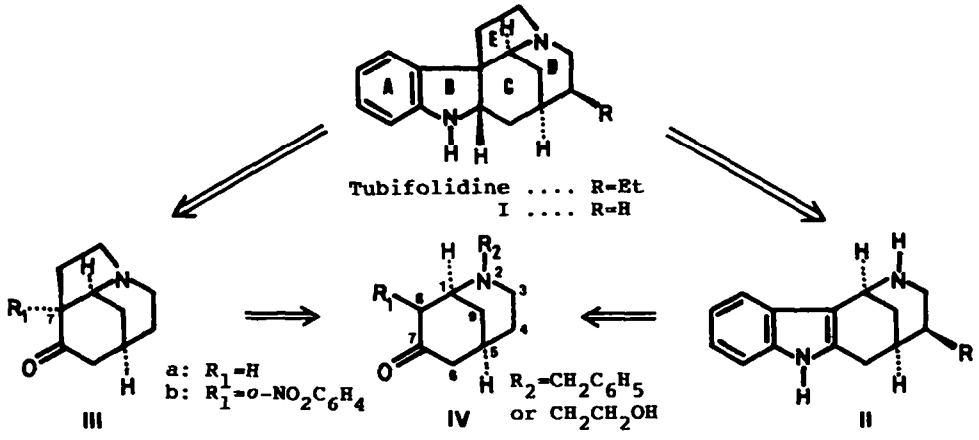
**Abstract** —— The first synthetic route to 8-aryl-2-azabicyclo-[3.3.1]nonan-7-ones (e.g. **5**) is reported. The synthesis involves acid cyclization of an appropriate 4-acetonyl-2-piperidinecarbonitrile (**4**) which, in turn, is obtained from the corresponding piperidine (**3**) by a modified Polonovski reaction. The *o*-nitrophenyl substituent of **3** is introduced by arylation of 4-piperidineacetoacetate **1** with *o*-fluoronitrobenzene followed by acid hydrolysis. The conversion of *α*-(*o*-nitrophenyl)ketone **5** to the bridged azocinoindole **7**, an intermediate in the synthesis of deethyltubifolidine, is also reported.

## INTRODUCTION

The synthesis of pentacyclic *Strychnos* indole alkaloids has been usually accomplished by transannular cyclization of tetracyclic compounds having the ring skeleton of stemmadenine.[2] During the last years, we have been involved in the development of new routes to these alkaloids. We have explored two different strategies: a) elaboration of the pyrrolidine E ring from a suitable hexahydro-1,5-methanoazocino-[4,3-*b*]indole (**II**), and b) formation of the indoline nucleus in a late synthetic step from an azatricyclic ketone (**IIIa**) possessing rings C, D, and E of *Strychnos* alkaloids. Whereas the first route has recently culminated in the total synthesis




Scheme I

of tubifolidine,[3] the second approach was ineffective since the Fischer indolization of **IIIa** failed to give the desired *Strychnos*-type regioisomer (I).[4]

This result prompted us to study an alternative way to construct the indoline nucleus, consisting in the reductive cyclization of a tricyclic ketone (**IIIb**) in which the bond between the quaternary C-7 center and the aryl group had been previously formed.[5] This ketone would be synthesized, in a similar manner than its C-7 unsubstituted analogue **IIIa**,[4,6] from an appropriately functionalized 2-azabicyclo[3.3.1]nonane derivative **IV**. This proposition implied, as preliminary requisite, the development of an efficient synthetic route to 8-aryl-2-azabicyclo[3.3.1]nonan-7-ones.

This paper deals with the preparation of the potential intermediate 8-(*o*-nitrophenyl)-2-azabicyclo[3.3.1]nonan-7-one **5** (**IVb**, $R_2$=$CH_2C_6H_5$) through the procedure that we have recently established for the synthesis of 2-azabicyclo[3.3.1]nonanes, which is based on the acid-promoted cyclization of 4-acetonyl-2-piperidinecarbonitriles.[1] Additionally, we report here the conversion of the above bicyclic intermediate **5** to tetracycle **7** (**II**, R=H), thereby establishing a new synthetic entry to hexahydro-1,5-methanoazocino[4,3-*b*]indoles. Until now, the synthesis of compounds having this tetracyclic ring system had been accomplished only by closure of the carbocyclic C ring, either by formation of $C_6$-$C_{6a}$[7,8] or $C_1$-$C_{11b}$ bonds.[9-11] Compound **7** had been previously elaborated into a pentacyclic *Strychnos*-type system by cyclization of the corresponding $N_b$-(2,2-dimethylthio)ethyl substituted derivative.[12]

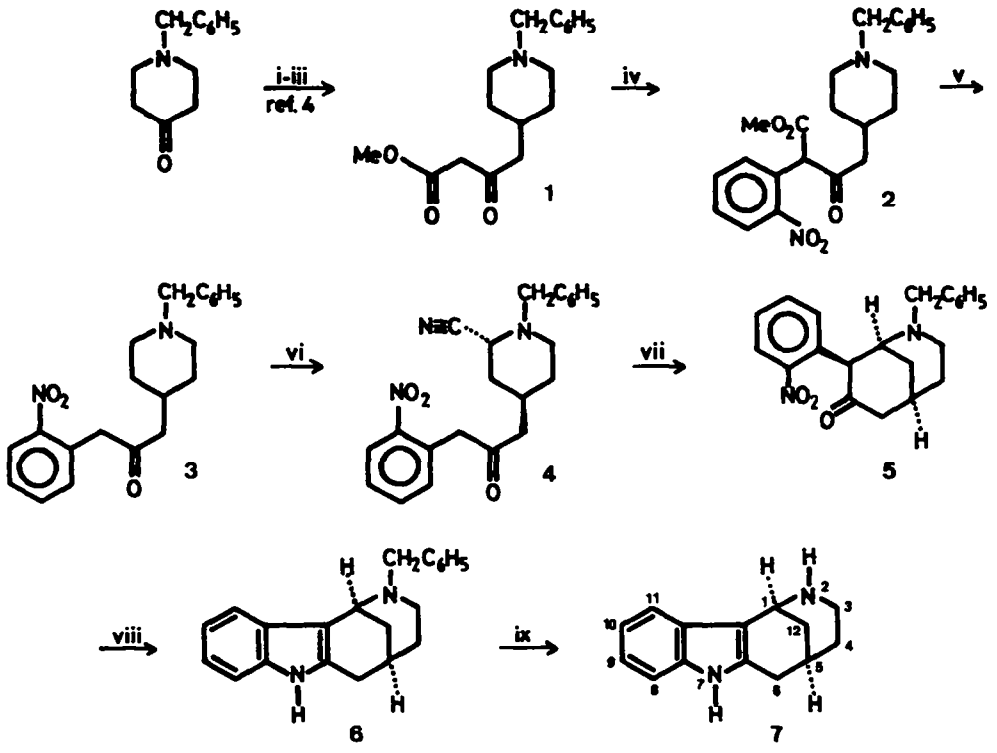
## RESULTS AND DISCUSSION

The reaction sequence adopted for the synthesis of the target compound **5** is outlined in Scheme II. The key steps of this synthesis are: a) introduction of the *o*-nitrophenyl substituent and b) closure of the carbocyclic ring.

Among the several methods available for preparing *o*-nitrobenzyl ketones[13-17] we chose that based on the nucleophilic substitution of halogen in *o*-fluoronitrobenzene by ß-keto ester anions followed by dealkoxycarbonylation of the resulting arylated ß-keto ester.[14a] In this manner we could take advantage of the easily accessible piperidineacetoacetate **1**, whose preparation had been previously effected in our laboratory.[4] Arylation of ß-keto ester **1** with *o*-fluoronitrobenzene was achieved in 44% yield by using potassium *tert*-butoxide as a base in hexamethylphosphoramide. Subsequent hydrolysis and decarboxylation of aryl ß-keto ester **2**, which appeared to be mainly enolic,[18] by treatment with 3 N hydrochloric acid gave nitrobenzyl ketone **3** in 86% yield.

Closure of the carbocyclic ring was effected by a Mannich-type reaction from 2-cyanopiperidine **4**, taking advantage of the fact that α-amino nitriles constitute latent forms of iminium ions. The conversion of piperidine **3** to the required 2-cyano derivative **4** (isolated in 70% yield as a single isomer) was carried out in a one-pot reaction[19] by successive treatment of **3** with *m*-chloroperbenzoic acid, trifluoroacetic anhydride, and potassium cyanide (Polonovski-Potier-Husson reaction[20]). Finally, treatment of 2-cyanopiperidine **4** with *p*-toluenesulfonic acid in refluxing toluene afforded the expected 8-aryl-2-azabicyclo[3.3.1]nonan-7-one derivative **5**.

The structure of **5** was inferred from its NMR data. Thus, a doublet at δ4.43 for the 8-H, a broad singlet at δ3.53 for the 1-H, and characteristic signals attributable to diastereotopic benzylic protons in the $^1$H-NMR spectrum clearly indicated that cyclization had occured. The relative stereochemistry at C-8, that implies the equatorial disposition of the aryl group, was established on the basis of the shielding of the benzylic carbon (-5.4 ppm) in the $^{13}$C-NMR spectrum, as



**Scheme II**

Reagents: (i) $(Et_2O)_2POCH_2COCH_3$, KOH, EtOH-$H_2O$; (ii) $H_2$/Pd-C, EtOH; (iii) $Me_2CO_3$, NaH, THF; (iv) *o*-$FC_6H_4NO_2$, *t*-BuOK, HMPA; (v) 3 N HCl; (vi) *m*-CPBA, $CH_2Cl_2$; then $(CF_3CO)_2O$; then aq. KCN, pH 5; (vii) TsOH, toluene; (viii) Fe, AcOH; (ix) $Pd(OH)_2$, EtOH.

compared with the bicyclic analogue lacking the aryl group (**IVa**, $R_2$=$CH_2C_6H_5$),[21,22] due to the steric crowding between the equatorial *o*-nitrophenyl substituent and the benzylic methylene. The absence of shielding $\gamma$-effects at C-6 and C-9 is in agreement with this stereochemical assignment. Moreover, the multiplicity of 8-H (sharp doublet with $J_{1,8}$= 4 Hz) in the $^1$H-NMR spectrum excludes the existence of long range W-type couplings, which should be observed if 8-H would be located equatorially.[22] Other noteworthy spectroscopic data of **5** were the low carbonyl absorption both in the IR (1680 $cm^{-1}$) and $^{13}$C-NMR spectra ($\delta$196.4).[23]

With a suitable method in hand for preparing 8-aryl-2-azabicyclo[3.3.1]nonan-7-ones, the next phase of our strategy, i.e. the elaboration of the pyrrolidine ring present in **IIIb** (see Scheme I), can be undertaken. This proposal, as well as the application of 8-(*o*-nitrophenyl)-2-azabicyclo[3.3.1]nonan-7-one derivatives to the synthesis of *Strychnos* indole alkaloids, is under study in our laboratory.

On the other hand, reductive cyclization of $\alpha$-(*o*-nitrophenyl)ketone **5** with iron in acetic acid[24,25] gave the tetracyclic base **6**, a compound that had been previously synthesized by a different route.[10a] Removal of the *N*-benzyl group by hydrogenolysis over Pearlman's catalyst[26] yielded the known secondary amine **7** (**II**, R=H),[27] an intermediate in our synthesis of deethyltubifolidine (**I**).[28] In this way, the synthesis of azocinoindole **7** further illustrates the usefulness of functionalized 2-azabicyclo[3.3.1]nonanes as synthetic intermediates.

## EXPERIMENTAL

*General.* $^1$H- and $^{13}$C-NMR spectra were recorded in $CDCl_3$ on a Varian XL-200 spectrometer. Chemical shifts are expressed in parts per million ($\delta$) relative to internal TMS. IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer and only noteworthy absorptions (reciprocal centimeters) are listed. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer. Flash column chromatography was carried out on $SiO_2$ (silica gel 60, 0.040-0.063 mm, Macherey-Nagel). TLC was performed on $SiO_2$ (silica gel 60 $F_{254}$, Macherey-Nagel), using 95:5 methylene chloride-methanol as developing solvent, and the spots were located with UV light or iodoplatinate reagent. Melting point was determined in a capillary tube on a CTP-MP 300 hotplate apparatus. 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 1-Benzyl-4-(o-nitrophenyl)-4-piperidineacetoacetate* (**2**). To a solution of ß-keto ester **1** (5.25 g, 18.1 mmol) in 30 ml of hexamethylphosphoramide maintained under nitrogen atmosphere was added potassium *tert*-butoxide (3.04 g, 27.1 mmol). After ten minutes the base was completely dissolved and *o*-fluoronitrobenzene (2.10 ml, 19.9 mmol) was slowly added giving a dark red solution almost immediately. The reaction mixture was stirred at 60-70°C for two hours, cooled, diluted with water, and extracted with ether. The combined ethereal extracts were exhaustively washed with brine, dried, and evaporated. Flash chromatography (99:1 methylene chloride-methanol) gave pure arylated ß-keto ester **2** (3.26 g, 44%) as a yellow oil; IR (NaCl): 1745 (weak, CO ester), 1720 (weak, CO ketone), 1680 (strong, CO enol ester), 1655 (strong, C=C enol), 1530 and 1350 ($NO_2$); $^1$H-NMR[29]: 1.15 (m, 2H, 3- and 5-Hax), 1.65 (m, 3H, 4-Hax, 3- and 5-Heq), 1.90 (tm, J = 12 Hz, 2H, 2- and 6-Hax), 1.96 (dd, J = 16 and 6.5 Hz, 1H, $CH_2CO$), 2.05 (dd, J = 16 and 7.5 Hz, 1H, $CH_2CO$), 2.82 (m, 2H, 2- and 6-Heq), 3.43 (s, 2H, $NCH_2Ar$), 3.63 (s, 3H, $OCH_3$), 7.2-7.4 (m, 6H, ArH), 7.55 (m, 2H, $NO_2$-ArH), 8.04 (d, J = 8 Hz, 1H, 3'-ArH); $^{13}$C-NMR[29]: 31.7 and 32.1 (3- and 5-C), 33.5 (4-C), 39.5 ($CH_2CO$), 51.9 ($OCH_3$), 53.6 and 53.7 (2- and 6-C), 63.5 ($NCH_2Ar$), 101.5 (=C-CO), 124.7 (3'-C), 126.9 (*p*-C), 128.1 (*o*-C), 128.7 (4'-C), 129.3 (*m*-C), 129.9 (1'-C), 132.9 (6'-C), 134.3 (5'-C), 138.3 (*ipso*-C), 149.6 (2'-C), 171.7 (HO-C=), 174.7 (COOMe); MS,*m/e* (relative intensity) 410 ($M^+$, 0.2), 204 (10), 172 (18), 159 (7), 146 (5), 120 (5), 92 (11), 91 (100), 83 (13), 77 (6), 70 (5), 69 (6), 57 (9), 44 (36). (Found: C, 67.66; H, 6.78; N, 6.55. Calcd. for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.39; N, 6.82).

*1-(1-Benzyl-4-piperidyl)-3-(o-nitrophenyl)-2-propanone* (**3**). A solution of ß-keto ester **2** (5.7 g 13 mmol) in 100 ml of 3N hydrochloric acid was refluxed for 3 h. After cooling, the reaction mixture was basified with aqueous 2N 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 (98:2, methylene chloride-methanol) yielded pure ketone **3** (3.93 g, 86%) as a dark red oil; IR (NaCl): 1710 (CO), 1520 and 1345 ($NO_2$); $^1$H-NMR: 1.37 (dq, J = 12, 12, 12 and 3 Hz, 2H, 3- and 5-Hax), 1.71 (dm, J = 12 Hz, 2H, 3- and 5-Heq), 1.8-2.0 (m, 1H, 4-Hax), 2.05 (td, J = 12, 12, and 2.5 Hz, 2H, 2- and 6-Hax), 2.53 (d, J = 6.5 Hz, 2H, $CH_2CO$), 2.90 (dm, J = 12 Hz, 2H, 2- and 6-Heq), 3.54 (s, 2H, $NCH_2Ar$), 4.08 (s, 2H, $ArCH_2CO$), 7.2-7.4 (m, 6H, ArH), 7.45 (td, J = 8 and 1.5 Hz, 1H, 4'-H), 7.59 (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: 31.5 (4-C), 32.0 (3- and 5-C), 48.5 and 49.2 ($CH_2COCH_2$), 53.5 (2- and 6-C), 63.3 ($NCH_2Ar$), 125.2 (3'-C), 127.1 (*p*-C), 128.2 (*o*-C), 128.4 (4'-C), 129.3 (*m*-C), 130.2 (1'-C), 133.5 (5'- and 6'-C), 138.2 (*ipso*-C), 149.0 (2'-C), 204.8 (CO). (Found: C, 70.13; H, 7.00; N, 7.43. Calcd. for $C_{21}H_{24}N_2O_3 \cdot 1/2H_2O$: C, 69.78; H, 6.97; N, 7.74).

trans-*1-Benzyl-4-[3-(o-nitrophenyl)acetonyl]-2-piperidinecarbonitrile* (**4**). A solution of *m*-chloroperbenzoic acid (Merck 85%, 2.38 g, 17.7 mmol) in dry methylene chloride (45 ml) was added over a few minutes to a stirred solution of ketone **3** (3.77 g, 10.7 mmol) in dry methylene chloride (45 ml) maintained at 0°C under argon atmosphere. Stirring was continued at 0°C for one hour. After the resulting solution had been cooled to -15°C, trifluoroacetic anhydride (5.95 ml, 42.8 mmol) was added dropwise and the mixture was stirred at -15°C for 1 hour and at room temperature for 15 min. Potassium cyanide (2.78 g, 42.8 mmol) in water (23 ml) was then added and the pH adjusted to 5 by the addition of solid sodium acetate. The two phase mixture was vigorously stirred for 30 min, basified with 10% aqueous sodium carbonate, and extracted with methylene chloride. The organic extracts were washed with water, dried, and evaporated. Flash chromatography (99.75:0.25 methylene chloride - methanol) gave pure nitrile **4** (2.81 g, 70%) as a yellow oil; IR: 2250 (CN), 1710 (CO), 1520 and 1350 ($NO_2$); $^1$H-NMR: 1.25-1.75 (m, 2H, 3- and 5-Hax), 1.82 (dm, J = 12 Hz, 1H, 5-Heq), 1.96 (dm, J = 12 Hz, 3-Heq), 2.30 (m, 1H, 4-Hax), 2.57 (d, J = 6.5 Hz, $CH_2CO$), 2.60 (m, 1H, 6-Hax), 2.95 (dm, J = 12 Hz, 1H, 6-Heq), 3.62 and 3.81 (2d, J = 13 Hz, 1H each, $NCH_2Ar$), 3.84 (br s, 1H, 2-Heq), 4.07 (s, 2H, $ArCH_2CO$), 7.20-7.54 (m, 7H, ArH), 7.60 (td, J = 8 and 1.5 Hz, 1H, 5'-H), 8.12 (dd, J = 8 and 1.5 Hz, 1H, 3'-H); $^{13}$C-NMR: 27.8 (4-C), 30.6 (5-C), 33.6 (3-C), 48.1 ($ArCH_2CO$), 48.2 (6-C), 49.5 ($COCH_2$), 51.5 (2-C), 60.2 ($NCH_2Ar$), 115.6 (CN), 125.2 (3'-C), 128.2 (*p*-C), 128.5 (4'-C), 128.7 (*o*-C), 129.5 (*m*-C), 130.1 (1'-C), 133.6 (5'- and 6'-C), 135.2 (*ipso*-C), 148.6 (2'-C), 203.7 (CO). (Found: C, 69.69; H, 6.16; N, 10.90. Calcd. for $C_{22}H_{23}N_3O_3$: C, 70.00; N, 6.14; N, 11.13).

(2RS,5SR,8RS)-*2-Benzyl-7-(o-nitrophenyl)-2-azabicyclo[3.3.1]nonan-7-one* (**5**). A mixture of amino nitrile **4** (2.81 g, 7.4 mmol) and *p*-toluenesulfonic acid monohydrate (3.5 g, 18.4 mmol) in toluene (65 ml) was refluxed under nitrogen, using a Dean-Stark apparatus, for 22 h. The mixture was cooled and basified with aqueous ammonium hydroxide. The organic layer was separated and the aqueous one was exhaustively extracted with methylene chloride. The combined organic extracts were dried and the solvent was removed. Flash chromatography (increase from 1% to 3% methanol-methylene chloride) afforded bicyclo **5** (984 mg, 38%). An analytical sample was obtained by recrystallization

from ether-acetone, colorless crystals: mp 119-120°C; IR ($CHCl_3$): 1680 (CO), 1520 and 1350 ($NO_2$); $^1$H-NMR: 1.36 (dm, J = 13.5 Hz, 1H, 4-Heq), 1.87 (dq, J = 13.5 Hz, 1H, 9-Hanti), 2.14 (ddd, J = 13.5, 13.5, and 4.5 Hz, 1H, 4-Hax), 2.37 (dq, J = 13.5 and 3 Hz, 1H, 9-Hsyn), 2.58-2.81 (m, 4H, 6-$CH_2$, 3-Heq and 5-Heq), 3.03 (ddd, J = 14, 13.5, and 3.5 Hz, 1H, 3-Hax), 3.53 (br s, 1H, 1-Heq), 3.68 and 3.79 (2d, J = 14 Hz, 1H each, $NCH_2Ar$), 4.43 (d, J = 4 Hz, 1H, 8-Hax), 6.91 4m, 2H, ArH), 7.13 (m, 3H, ArH), 7.45 (td, J = 8 and 1.5 Hz, 4-H), 7.64 (td, J = 8 and 1.5 Hz, 5-H), 7.74 (dd, J = 8 and 1.5 Hz, 6-H), 7.87 (dd, J = 8 and 1.5 Hz, 3-H); $^{13}$C-NMR: 32.7 (4-C), 33.0 (5-C), 35.8 (9-C), 44.5 (3-C), 46.4 (6-C), 54.0 ($NCH_2Ar$), 56.0 (1-C), 60.5 (8-C), 124.3 (3-C), 127.0 (*p*-C), 128.1 and 128.4 (*o*- and *m*-C), 128.8 (4-C), 131.6 and 133.3 (5- and 6-C), 139.3 and 140.0 (1- and *ipso*-C), 148.6 (2-C), 196.4 (CO); MS, *m/e* (relative intensity): 350 ($M^+$, 0.1), 172 (3), 159 (3), 120 (14), 107 (9), 106 (9), 91 (100), 83 (5), 77 (7), 65 (13), 63 (4), 55 (7), 44 (7). (Found: C, 71.84; H, 6.24; N, 7.88. Calcd. for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99).

*2-Benzyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole* (**6**). In a one-necked flask were placed *o*-nitrophenyl ketone **5** (150 mg, 0.43 mmol), iron powder (325 mesh, 84 mg, 1.5 mmol), acetic acid (0.17 ml, 3 mmol), and 20 ml of 80:20 (v/v) ethanol-water. The mixture was refluxed with stirring for 2 h under argon atmosphere. The reaction mixture was cooled, decanted, and the ethanol was evaporated. The residue was basified with aqueous potassium carbonate solution and extracted with methylene chloride. Evaporation of the dried organic extracts gave an oil which was purified by flash column chromatography ($Al_2O_3$, methylene chloride) to yield **6** (91 mg, 70%). The spectral data(IR, $^1$H-NMR) and the TLC Rf values for this product were identical to those of compound **6** prepared by an independent synthesis.[10a]

*1,2,3,4,5,6-Hexahydro-1,5-methanoazocino[4,3-b]indole* (**7**). A suspension of benzyl derivative **6** (103 mg, 0.34 mmol) and 20% $Pd(OH)_2$ (Pearlman's catalyst) (34 mg) in methanol (8 ml) was hydrogenated until total disappearance of the starting compound was observed by TLC. After 24 h additional 20% $Pd(OH)_2$ was added. The catalyst was removed by filtration through Celite and the solvent evaporated. The residue was dissolved in methylene chloride and washed with aqueous 10% sodium carbonate solution. Evaporation of the dried extract gave an oil which was chromatographed ($SiO_2$, 95:3:2 ether-acetone-diethylamine) to afford the secondary amine **7** (35 mg, 50%), identical ($^1$H-NMR and TLC Rf values) with an authentic sample.[27]

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